TOTAL SYNTHESIS OF VINIGROL

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by

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TOTAL SYNTHESIS OF VINIGROL

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Vinigrol, an unusual diterpene, was isolated by Hashimoto and co-workers in 1987, from the fungal strain *Virgaria nigra* F-5408. Biological test of vinigrol has revealed a number of interesting properties, such as antihypertension and platelet aggregation inhibition. Vinigrol is also a tumor necrosis factor (TNF) antagonist. The promising biological activities, combined with its unique terpene structure have attracted significant attention from the synthetic community. Herein, a total synthesis of vinigrol is described. The synthesis demonstrates the power of oxidative dearomatization and intramolecular Diels-Alder cycloaddition to construct complex molecules. Additionally, a few new synthetic strategies and tactics were developed, such as selenium dioxide mediated olefin isomerization and oxidation, stereoselective installation of an isopropyl group and strategic applications and deprotection of trifluoroethyl ethers.

BIOGRAPHICAL SKETCH

Qingliang Yang was born in a small village in Hubei province, China, where the Yangtze River flows through. After high school, he moved up along the river to Chengdu, Sichuan where he was admitted to Sichuan University and studied environmental chemistry at the department of chemistry. Allured by the fascinating chemical research conducted in the western world, after college he crossed the Pacific Ocean and landed in Wichita, Kansas. He studied organic synthesis and medicinal chemistry with Professor William Groutas at Wichita State University. Three years later he moved to upstate New York and worked as a medicinal chemist at AMRI, Albany. He decided to return to graduate school in the belief that to excel as a medicinal chemist, one needs to be a great synthetic chemist first. Therefore he joined the Njardarson group at Cornell University to work on natural product total synthesis. Now, after completion of the total synthesis of vinigrol, he looks forward to new adventures life brings him.

In memory of

my parents and grandparents

ACKNOWLEDGMENTS

First of all, I would like to thank my research advisor, Professor Jon Njardarson, who has guided the vinigrol project from the initial idea to the final reaction. I appreciate his belief in me and most importantly, his confidence and always positive attitude toward difficulties in the synthesis. I would also like to thank Dr. Jason G.M. Morton for the groundbreaking work of this project, Dr. Cristian Draghici for the front-to-back radical approach that he undertook and for realizing the Heck-Stille cascade, Dr. Fang Li for the advanced intermediates of the final route that he produced and Brandon Smith and Pradipta Das for the characterizations of compounds of radical approaches. Without their effort and determination, the project could not have been a success. I also benefited from working with three very skilled chemists during my time at Cornell, Dr. Matthew Brichacek, Dr. Nicholas McGrath and Dr. Daniel Mack. They taught me countless lessons in the lab and their insights into the project and suggestions are greatly appreciated.

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LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
AIBN	1,1′-Azobis(cyclohexanecarbonitrile)
CDMT	2-Chloro-4,6-dimethoxy-1,3,5-triazine
m-CPBA	meta-Chloroperoxybenzoic acid
Cp	Cyclopentadienyl
CSA	(+/–)-Camphor-10-sulfonic acid
DATMP	Diethylaluminum 2,2,6,6-tetramethylpiperidide
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
o-DCB	*ortho*-Dichlorobenzene
DCE	1,2-Dichloroethene
DCM	Dichloromethane
DIAD	Diisopropyl azodicarboxylate
DIBAL	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	Dess-Martin periodinane
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HMPA	Hexamethylphosphoramide
IMDA	Intramolecular Diels-Alder
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
Lg	Leaving group
Ms	Methanesulfonyl

MoOPH	$MoO_5 \cdot Py \cdot HMPA$
NIS	*N*-Iodosuccinimide
NMM	*N*-Methylmorpholine
NMO	*N*-Methylmorpholine-*N*-oxide
OD	Oxidative dearomatization
PIDA	Phenyliodine(III) diacetate, $PhI(OAc)_2$
PIFA	Phenyliodine(III) bis(trifluoroacetate), $PhI(OCOCF_3)_2$
Py	Pyridine
RCM	Ring closing metathesis
r.t.	Room temperature
TBAF	Tetra-*n*-butylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
Tf	Trifluoromethanesulfonyl

Chapter 1

Introduction

1.1 Isolation and Biological Activity

Vinigrol (**1.1**, Figure 1.1), a novel diterpenoid, was first isolated in 1987 by Hashimoto, Ando and coworkers from a fungus strain, *Virgaria nigra* F-5408 in Japan.[1] Its structure was determined by using spectroscopic measurements (MS, IR, NMR and CD) and X-ray crystal analysis of its derivatives.

Vinigrol became of interest initially because of its antihypertensive and platelet aggregation inhibition properties.[2] It was discovered that when injected intravenously in anesthetized normotensive rats, vinigrol decreased arterial blood pressure by 20% at a dose of 100 mg/kg. Given orally to spontaneously hypertensive rats, a 15% blood pressure reduction was observed at 2 mg/kg and the effect lasted over 6 hours. Vinigrol inhibited the platelet aggregation induced with epinephrine or platelet activating factor. The IC_{50} values are 1.7×10^{-8} M and 4.4×10^{-7} M on rabbit platelet and 5.2×10^{-8} M and 3.3×10^{-8} M on human platelet for each aggregation agent, respectively. However, vinigrol did not exhibit any inhibitory activity on ADP, thrombin and collagen induced rabbit platelet aggregation and neither revealed any inhibitory effect on ADP induced human platelet aggregation at 1×10^{-6} M. Studies revealed that vinigrol is a Ca^{2+} agonist showing inhibitory effects on Ca^{2+} movement at lower concentrations. However, further experimentation is required to conclusively define the mode of action of vinigrol on calcium channels and also to clarify the mechanism of its antihypertensive activity.

In addition, vinigrol was shown to function as a potential tumor necrosis factor (TNF) antagonist agent.[3] TNF is a protein which induces necrosis of tumor cells and acts as a mediator in the immune system. Blocking the action of TNF could therefore treat endotoxic shock, inflammation, muscle atrophy (cachexia) or inhibit the progression from AIDS-related complex to AIDS. In in-vitro binding studies on HL60

cells, vinigrol at a concentration of 310 mM displayed 100% inhibition of [^{125}I]-TNF binding at 2.1 nM. A significant reduction of TNF-induced cytotoxicity on L929 cells was also observed. This discovery stimulated further investigations on vinigrol applications. In 1995, Fujisawa Pharmaceutical Company Limited disclosed that vinigrol could be used as an alternative therapy for the treatment of HIV infectious diseases.[4] Later, more studies showed that vinigrol could be used to treat inflammatory diseases, arthritic disorders and neurological diseases.[5] Further investigations revealed that some derivatives of vinigrol also have GM-CSF (granulocyte-macrophage colony-stimulating factor)-like activity, immunopotentiation activity, and antitumor activity.[6]

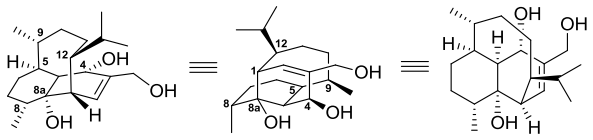


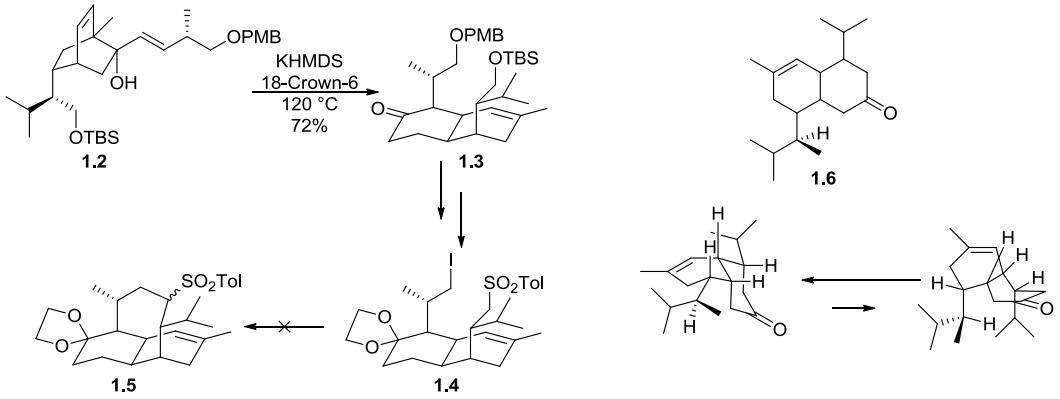
Figure 1.1. Vinigrol

1.2 Prior Art

From a synthetic perspective, vinigrol possesses a unique tricyclic core containing a *cis*-fused [4.4.0] system bridged by an eight-membered ring with eight contiguous stereocenters. This unprecedented architecture, coupled with its promising biological profile, has attracted significant attention from the synthetic community. Over the past two decades, tremendous efforts towards its total synthesis have been executed, including studies from the Paquette,[7] Corey,[8] Mehta,[9] Matsuda,[10] Fallis,[11] Hanna,[12] Baran[13] and Barriault[14] groups. In addition, two comprehensive reviews describing these efforts are available in the literature.[15]

The Paquette group reported an anionic oxy-Cope reaction to construct the *cis*-decalin portion of vinigrol (**1.3**) from a bicyclo[2.2.2]octenol precursor (**1.2**) (Scheme

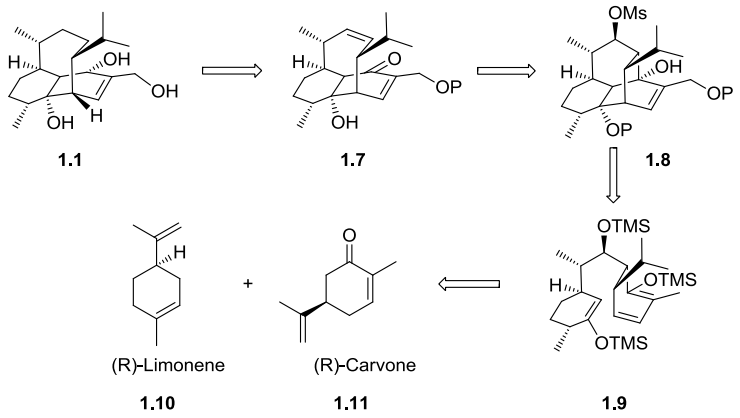
1.1). The initial strategy for the formation of the eight-membered ring was based on an intramolecular S_N2 cyclization. Subjection of substrate **1.2**, prepared from (*S*)-4-isopropyl-2-oxazolidinone in 11 steps, to KHMDS and 18-crown-6 under thermal conditions afforded **1.3** in 72% yield. Subsequently, compound **1.3** was converted to cyclization precursor **1.4** using a series of standard manipulations. Unfortunately, all attempts to construct the eight-membered ring were met with failure. X-ray analysis of **1.4** revealed that both decalin side chains are locked equatorially, positioning the nucleophilic center far from the electrophilic center for productive bond formation. Indeed, *ab initio* calculations of a model compound **1.6** revealed a largely unfavorable equilibrium between the two conformers, with the major diequatorial conformer lacking the stereoalignment needed for ring closure.



Scheme 1.1. Paquette's Approach toward Vinigrol

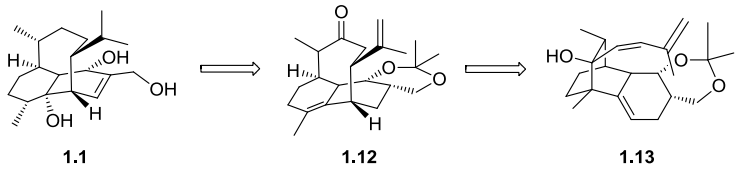
Unable to meet the conformational requirements for an anionic S_N2 cyclization, the group explored other eight-membered ring formation strategies, such as ring-closing olefin metathesis, radical cyclization, ring contraction, and Dieckman reaction. However, all methods proved to be unsuccessful.

The Corey group envisioned that the tricyclic core of vinigrol could be generated *via* an intramolecular Diels-Alder reaction of **1.9** followed by a Grob fragmentation of cycloadduct **1.8** to afford **1.7** (Scheme 1.2). For this purpose, the Diels-Alder precursor **1.9** was synthesized from (*R*)-limonene in six steps. Unfortunately, all attempts at realizing the proposed Diels-Alder reaction were unsuccessful and resulted only in isomerization of the trisubstituted enol ether to the thermodynamically more favorable tetrasubstituted isomer. The electron-rich nature of both diene and dienophile, as well as the steric congestion in the transition state, were attributed to the failure of the intramolecular cycloaddition. The group also investigated a series of intermolecular inverse electron-demand Diels-Alder routes, all of which proved to be fruitless.

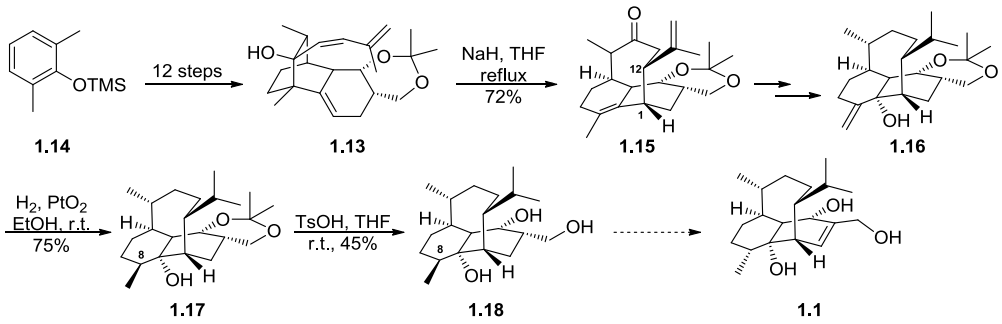


Scheme 1.2. Corey's Approach toward Vinigrol

In 1993, the Hanna group reported the first construction of the tricyclic core of vinigrol. In this synthesis, the oxygenated tricyclic skeleton (**1.12)** of vinigrol was assembled *via* an anionic oxy-Cope rearrangement from a tricyclic vinyl carbinol precusor, such as **1.13** (Scheme 1.3).



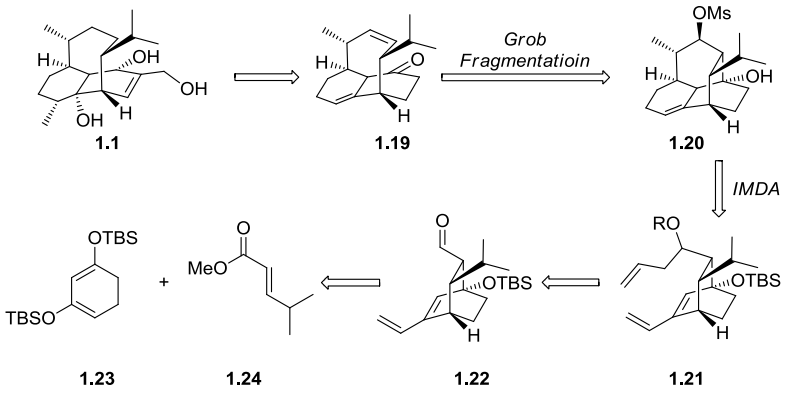
Scheme 1.3. Hanna's Approach toward Vinigrol



Scheme 1.4. Synthesis of *epi*-C8-Dihydrovinigrol

Compound **1.13** was prepared in 12 steps form silyl protected phenol **1.14** (Scheme 1.4). The proposed anionic oxy-Cope rearrangement proceeded smoothly after exposure of alcohol **1.13** to sodium hydride under reflux, delivering the tricyclic ketone **1.15** in good yield. In one nice operation, construction of the eight-membered ring and introduction of isopropenyl group at C12 with the correct stereochemistry were achieved. Following a series of functional group manipulations, allylic alcohol **1.16** was then obtained. Discouragingly, all attempts to reduce the exocyclic olefin of **1.16** resulted in the undesired C8 epimer. It appeared that in this reaction, addition of hydrogen occurred from the same side of hydroxyl group. Due to the presence of the carbon bridge, the approach of the catalyst from the other side was impeded by the severe steric hindrance. Subsequently, Hanna and his team were able to demonstrate that **1.17** could be hydrolyzed to *epi*-C8-dihydrovinigrol **1.18**, a derivative of the natural product.

In the spirit of Corey's approach, Baran's successful total synthesis of vinigrol similarly relied on a key intramolecular Diels-Alder reaction (IMDA) and subsequent Grob fragmentation to construct the tricyclic core from intermediate **1.21** (Scheme 1.5).

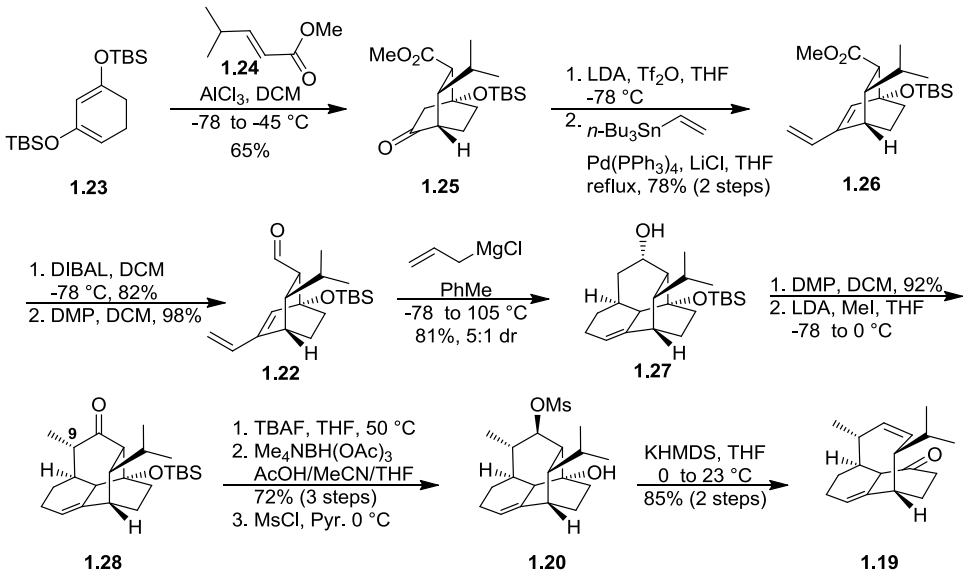


Scheme 1.5. Baran's Approach toward Vinigrol

The synthesis began with a Diels-Alder reaction between a *bis*(silyloxy)diene (**1.23**) and (*E*)-methyl 4-methyl-2-pentenoate (**1.24**) to install the initial bicycle in reasonable yield and diastereomeric excess (Scheme 1.6). To examine the key intramolecular Diels-Alder reaction, the diene unit (**1.26**) was introduced by coupling tributylvinylstannane with the corresponding enol triflate of **1.25**. The dienophile was installed by converting the bridge ester to an aldehyde, followed by addition of allylmagnesium chloride. Remarkably, the resultant triene underwent the desired Diels-Alder reaction under thermal conditions and generated the tetracyclic framework (**1.27**). Although neither the diene nor the dienophile are electronically activated, Baran postulated that this unprecedented reactivity originated from a combination of preorganization, diene strain, and tether stabilization of the substrate.[16]

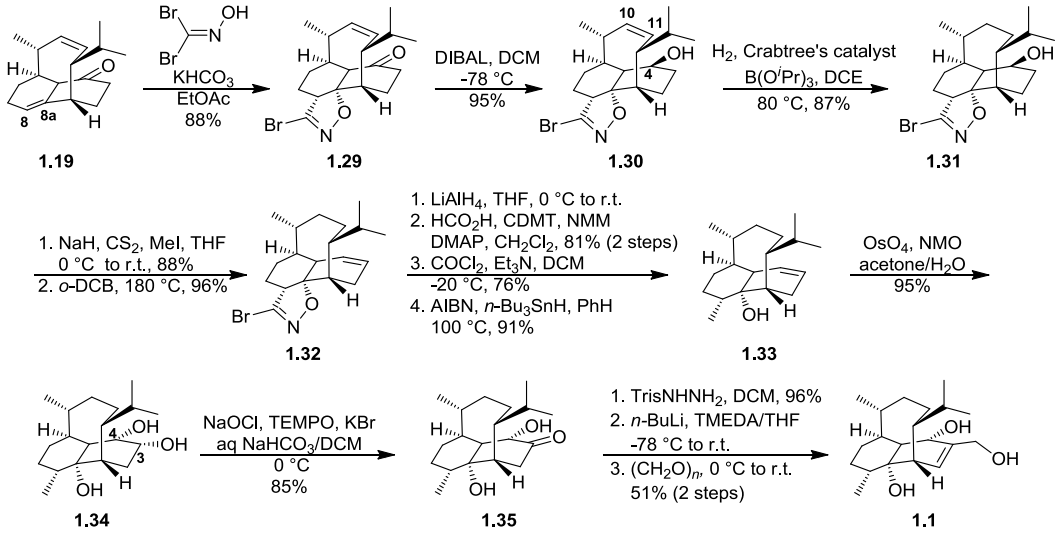
The C9 methyl group was diastereoselectively installed by alkylation after oxidation of the alcohol. Silyl group removal, directed reduction of the ketone and

mesylation provided the Grob fragmentation precursor **1.20**. A final base assisted Grob fragmentation efficiently afforded the tricyclic core (**1.19**).



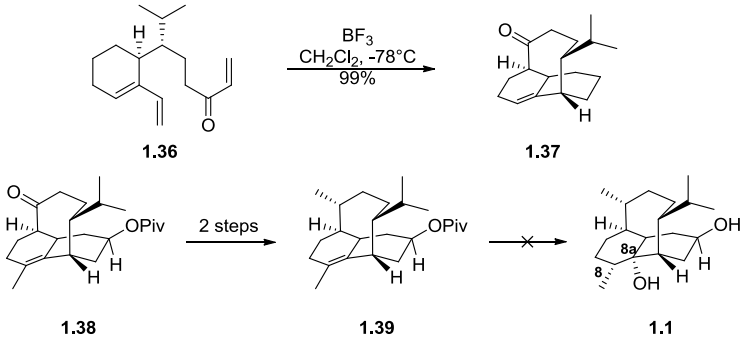
Scheme 1.6. Synthesis of Tricyclic Core

Due to the congested structural core of vinigrol, installation of the few remaining groups proved to be rather challenging (Scheme 1.7). Eventually, the C8 methyl and C8a hydroxyl groups were incorporated by an unusual [3+2] cycloaddition of **1.19** with dibromoformaldooxime and subsequent reduction and deamination of the corresponding isocyanide (**1.32**). During this process, the C10-11 double bond was reduced by hydrogenation. The installation of the C4 alcohol was also accomplished in a multi-step fashion, including a reduction of ketone **1.29**, followed by dehydration of the resultant epimeric alcohol (**1.31**) and substrate controlled dihydroxylation of the alkene (**1.33**). Lastly, the group utilized the Shapiro reaction to deliver the primary allylic alcohol after first selectively oxidizing the C3 alcohol (**1.34**) to ketone (**1.35**) with NaOCl and catalytic amount of TEMPO. Nearly 20 years after its isolation, the Baran group was able to complete the first total synthesis of vinigrol.



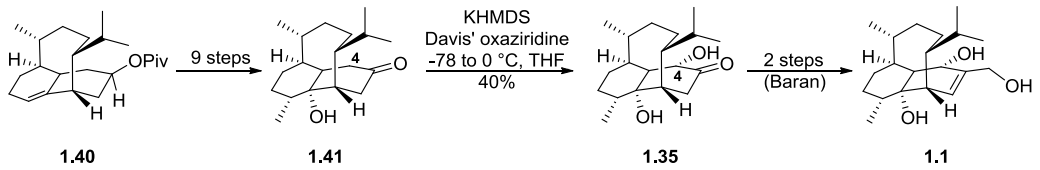
Scheme 1.7. Completion of the Total Synthesis

In 2007, the Barriault group reported a highly regioselective intramolecular Diels-Alder reaction of **1.36** to construct the tricyclic core of vinigrol (**1.37**) (Scheme 1.8). However, the natural product could not be accessed from **1.37**. Thus, a functionalized core **1.39** was synthesized. Unfortunately, all attempts to install the *trans* C8 methyl and C8a hydroxyl groups, including cycloaddition, epoxide opening, hydration, or by an ene reaction with singlet oxygen, failed.



Scheme 1.8. Barriault's Apporach toward Vinigrol

Inspired by the work of Baran, a des-methyl analogue of **1.39** was synthesized (**1.40**). Using Baran's solution, **1.40** was converted to **1.41** (Scheme 1.9). After the ketone was oxidized to the hydroxyl ketone (**1.35**), the formal synthesis of vinigrol was accomplished.



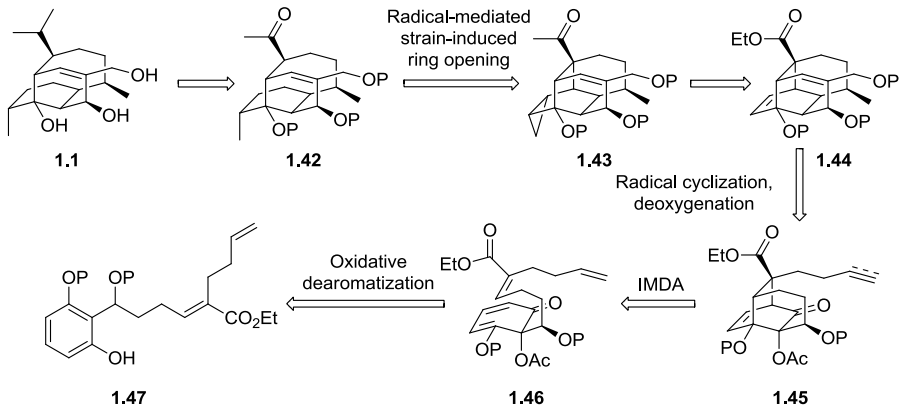
Scheme 1.9. Formal Synthesis of Vinigrol

It appears, from these approaches, that the major problem of achieving the total synthesis of vinigrol lies not only in the construction of the tricyclic core, but also in the transformation of functional groups present in this very congested structure. Nevertheless, three groups have now developed synthetic strategies that overcome the challenges of accessing this complex molecular scaffold; among which Baran's first total synthesis stands as a landmark achievement.

1.3 Initial Efforts from the Njardarson Group[17]

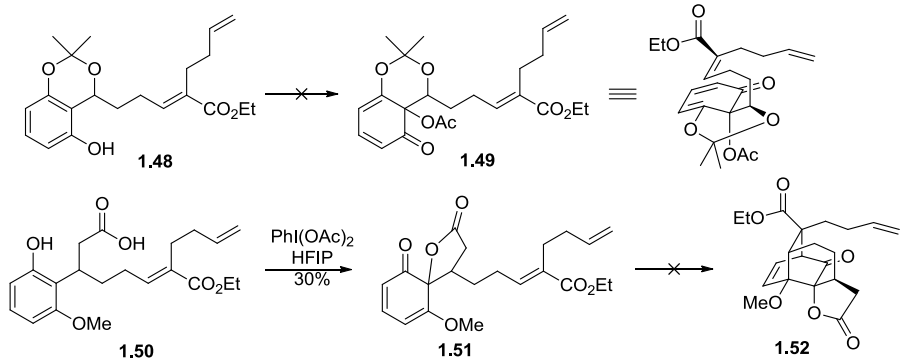
Synthetic efforts toward the total synthesis of vinigrol were initiated by Dr. Jason Morton in the Njardarson group. The first retrosynthetic strategy involved the construction of an advanced vinigrol precursor **1.42** (Scheme 1.9). Due to the fact that a direct contraction of the eight-membered ring would be relatively infeasible, it was envisioned that the selective bond cleavage of a bicyclo[2.2.2]octane system as in **1.43**, would 'unravel' the latent cyclooctane. Functional group manipulations would afford **1.44**, which could be generated from a 6-*exo-trig* or 6-*exo-dig* ring-closure and deoxygenation of **1.45**. This bicyclic scaffold would arise from the intramolecular

Diels-Alder cycloaddition of a diene containing *o*-benzoquinol **1.46**, itself generated *via* oxidative dearomatization of a suitably substituted phenol **1.47**.



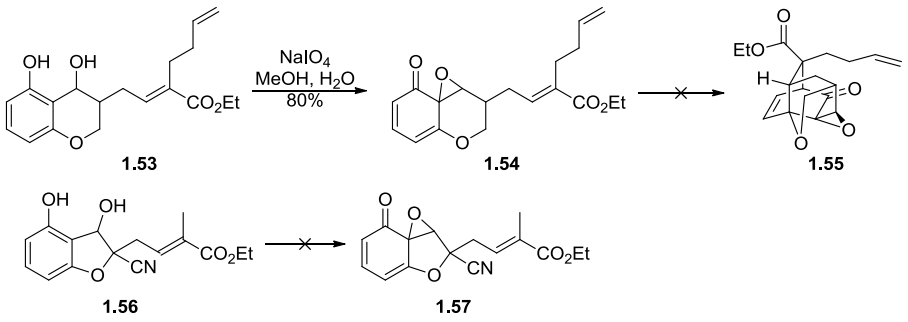
Scheme 1.10. Njardarson's Wessely Oxidation Approach

Unfortunately, the selective Wessely oxidative dearomatization (**1.49**, Scheme 1.11) turned out to be rather difficult, despite extensive evaluation of suitable oxidants, solvents and temperatures. Although modification of the substrate in order to intramolecularly deliver the nucleophile at the proper position proved to be successful (**1.51**), the following Diels-Alder reaction failed to afford any desired product (**1.52**).



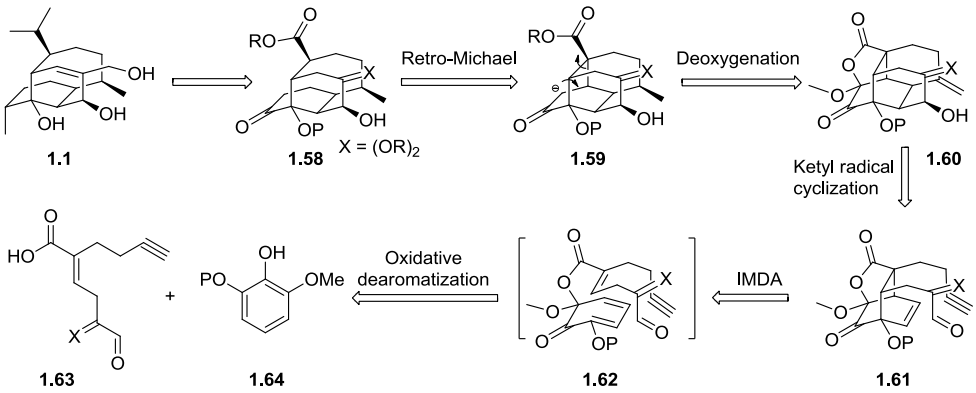
Scheme 1.11. Wessely Oxidation Attempts

A similar approach using an Adler-Becker oxidative dearomatization protocol was also pursued, but still without success (Scheme 1.12).



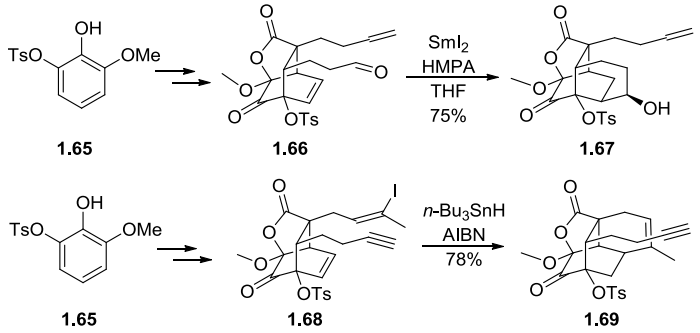
Scheme 1.12. Adler-Becker Oxidation Attempts

Having encountered difficulties with both the oxidative dearomatization and the Diels-Alder cycloaddition, a more robust route that would prove to successfully address both limitations was developed (Scheme 1.13). In this strategy, the core of vinigrol would be accessible from a retro-Michael reaction of **1.59**. In turn, **1.59** would be derived from deoxygenation of **1.60**, which would be delivered by a tandem 6-*exo* radical cyclization of **1.61**. This intermediate would be assembled from oxidative dearomatization and intramolecular Diels-Alder union of pyrogallol derivative **1.64** and arylic acid **1.63**.



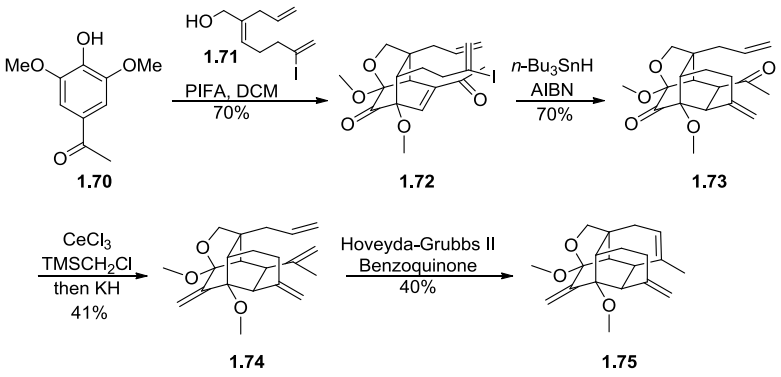
Scheme 1.13. Njardarson's Pyrogallol Approach

As expected, the oxidative dearomatization and intramolecular Diels-Alder sequence proceeded smoothly. However, the tandem cyclization failed to produce the desired outcome (Scheme 1.14). The second radical cyclization proved to be very challenging, which was perhaps not surprising in retrospect, considering the compact nature of the tetracyclic core of vinigrol.



Scheme 1.14. Tandem Radical Attempts

Due to the difficulty of realizing the tandem radical cyclization, a stepwise route that involved a sequential, rather than simultaneous, cyclization process was evaluated (Scheme 1.15). Cyclization substrate **1.72** was constructed using the oxidative dearomatization and intramolecular Diels-Alder strategy. Delightfully, treatment of **1.72** with *n*-Bu_3SnH and AIBN provided the monocyclized adduct **1.73**, with the desired stereochemistry for further cyclization. The ketone was then olefinated (**1.74**) and successfully cyclized under RCM conditions despite significant steric hindrance. Thereby, the vinigrol core **1.75** was constructed in 4 steps from commercially available starting material. A route based on this successful strategy toward vinigrol was immediately explored, which is the subject of the following chapters.



Scheme 1.15. Stepwise Radical Approach

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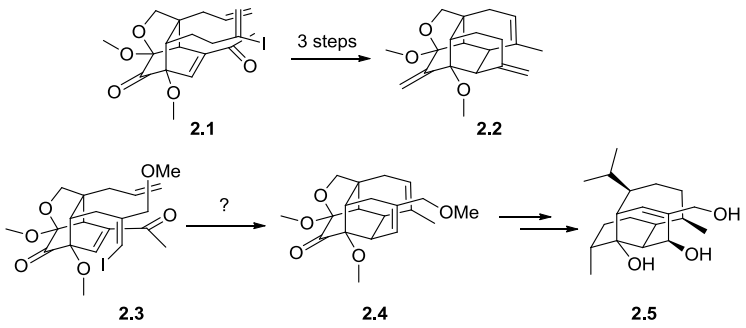
Chapter 2

Radical Approaches to Construct the Vinigrol Core

2.1 Synthetic Strategy

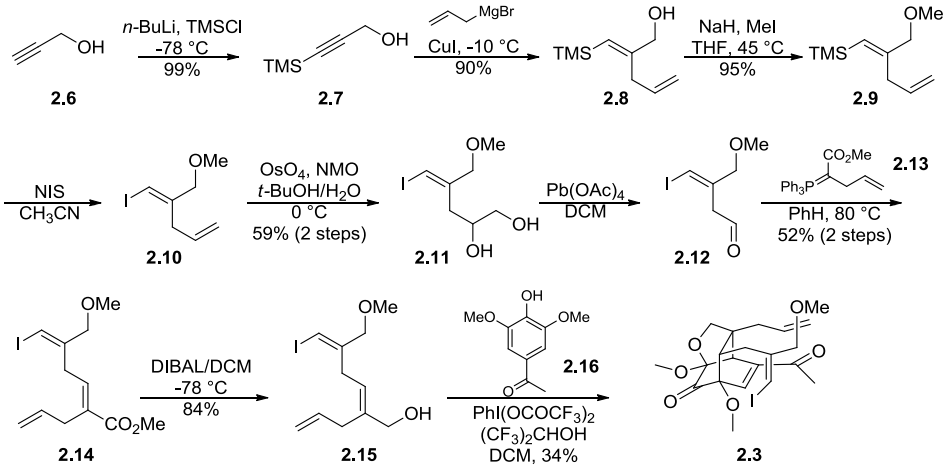
Base on earlier work in the Njardarson group, the vinigrol tetracyclic core could be constructed utilizing a stepwise cyclization strategy. Inspired by the success of synthesizing **2.2**, we set out to realize the same for precursor **2.3** (Scheme 2.1). It was hoped that this strategy could also be applied to the more functionalized substrate.



Scheme 2.1. Modification of the Stepwise Cyclization Substrate

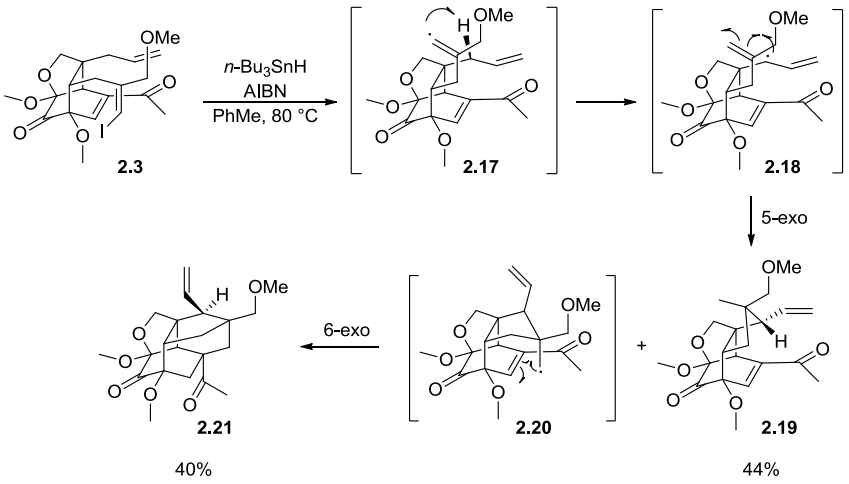
2.2 Results and Discussion

Preparation of cyclization precursor **2.3** commenced with the synthesis of known compound **2.9**[1] (Scheme 2.2). First, propargyl alcohol **2.6** was selectively trimethylsilylated (**2.7**). After cuprate addition, the resultant alcohol **2.8** was methylated to provide **2.9** in excellent yield. Iododesilylation of **2.9** afforded vinyl iodide **2.10**, which was then dihydoxylated to afford diol **2.11**. Oxidative cleavage of the diol and the subsequent *E*-selective Wittig reaction with phosphorane **2.13**[2] furnished **2.14**. Alcohol **2.15** was obtained by reduction of the ester, which was then coupled with commercially available phenol **2.16** using the same oxidative dearomatization and intramolecular Diels-Alder (OD/IMDA) protocol. Thus, the cyclization precursor **2.3** was prepared in fairly good yields.



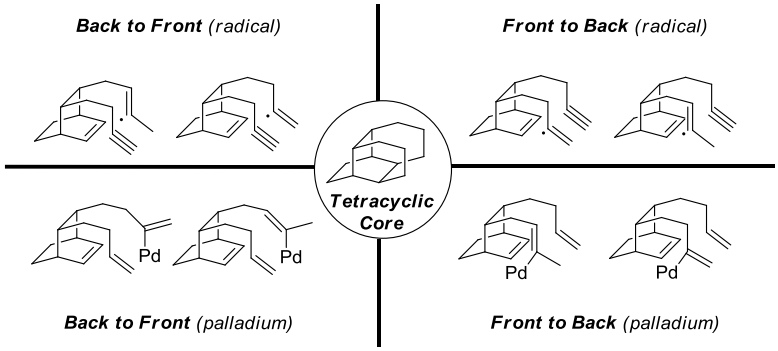
Scheme 2.2. Synthesis of the Cyclization Precursor

Product **2.3** was then submitted to radical cyclization conditions (AIBN or Et_3B/O_2 as initiators). Surprisingly, none of the desired cyclization product was detected. 2D-NMR analyses of the isolated products suggested that the initially formed radical **2.17** underwent, instead of a 6-*exo* cyclization, a 1,7-hydrogen abstraction of the adjacent allylic hydrogen. Subsequent radical cyclization afforded products **2.19** and **2.21** (Scheme 2.3).[3] Attempts to selectively mask the vinyl group and inhibit the unwanted hydrogen abstraction, such as hydrogenation, hydroboration, or epoxidation, were made, but these efforts met with no success.



Scheme 2.3. Unexpected Hydrogen Abstraction

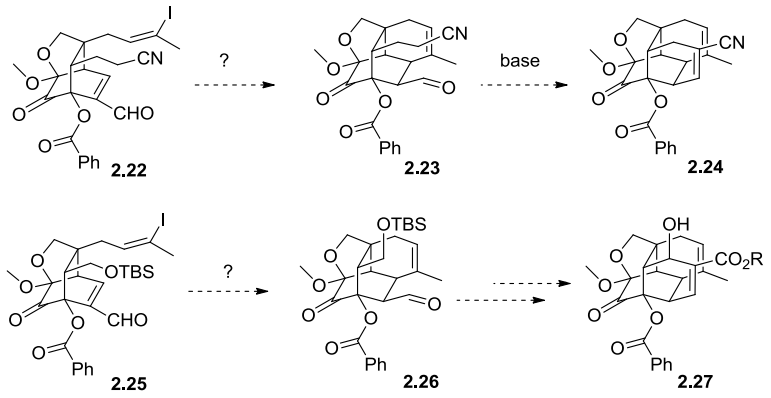
Disappointed by the unexpected hydrogen abstraction, we decided to seek alternative ways to construct the vinigrol tetracyclic core. Four different generic cyclization models, relying on either radical or palladium tandem 6-*exo* conditions, are shown in Scheme 2.4. The models differ only in the substitution pattern of the initiating species and whether the cyclization cascade starts from the back or from the front.



Scheme 2.4. Cyclization Options

Before yielding on the radical approach, radical cyclizations proceeding from back to front were also evaluated (Scheme 2.5). Compounds **2.22** and **2.25** would be

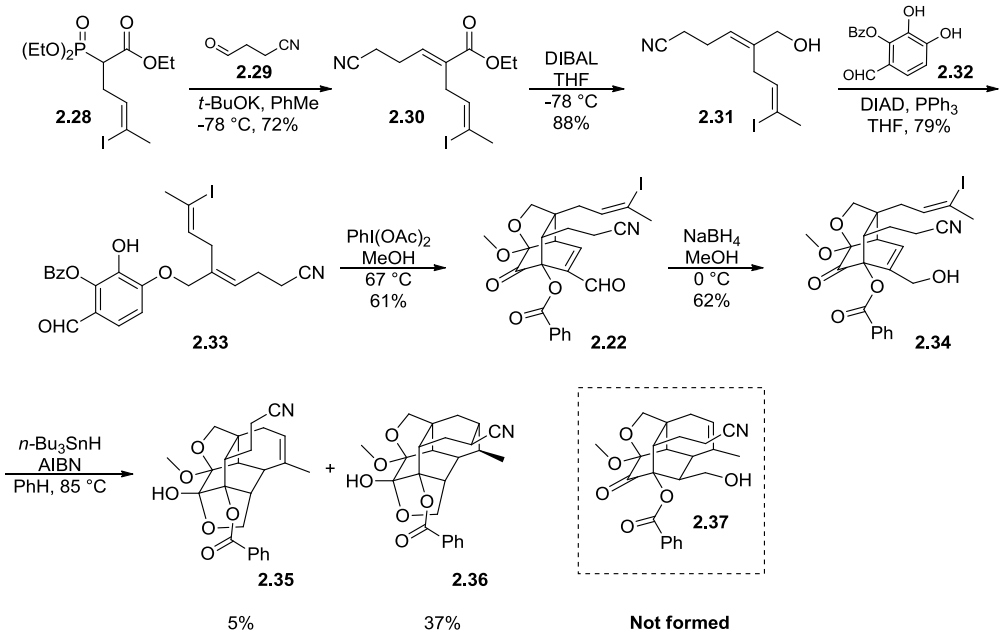
suitable cyclization precursors to test this idea. As having been shown previously, vinyl radicals are very reactive and could cyclize efficiently.[4] The front aldehyde, like the ketone in **2.1**, could serve as a synthetic handle to close the second ring.



Scheme 2.5. Proposed Substrates for Back-to-Front Radical Cyclizations

The synthesis of **2.22** commenced with Horner-Wadsworth-Emmons olefination between known phosphonate **2.28**[5] and aldehyde **2.29**[6] (Scheme 2.6). After DIBAL reduction and Mitsunobu coupling with **2.32**,[7] oxidative dearomatization precursor **2.33** was ready for the first key step. Careful screening of oxidants (phenyliodonium diacetate (PIDA) and phenyliodonium bis(trifluoroacetate) (PIFA)), solvents (THF, DCM, toluene, and MeOH), reaction temperatures and reagent addition rates (slow addition and one-portion addition) yielded an optimal OD/IMDA reaction procedure. By slowly adding PIDA to the pre-heated (refluxing) methanol solution of **2.33**, cycloadduct **2.22** could be afforded directly in good yield. Unfortunately, the radical cyclization conditions did not afford any desired product. The aldehyde was then converted to alcohol **2.34**, in the belief that the aldehyde was problematic. Exposure of **2.34** to radical reaction conditions (*n*-Bu_3SnH and AIBN, 85 °C) afforded two products (**2.35** and **2.36**, structures were assigned on the basis of 2D NMR and MS analyses**)** after silica gel column chromatography. However, no

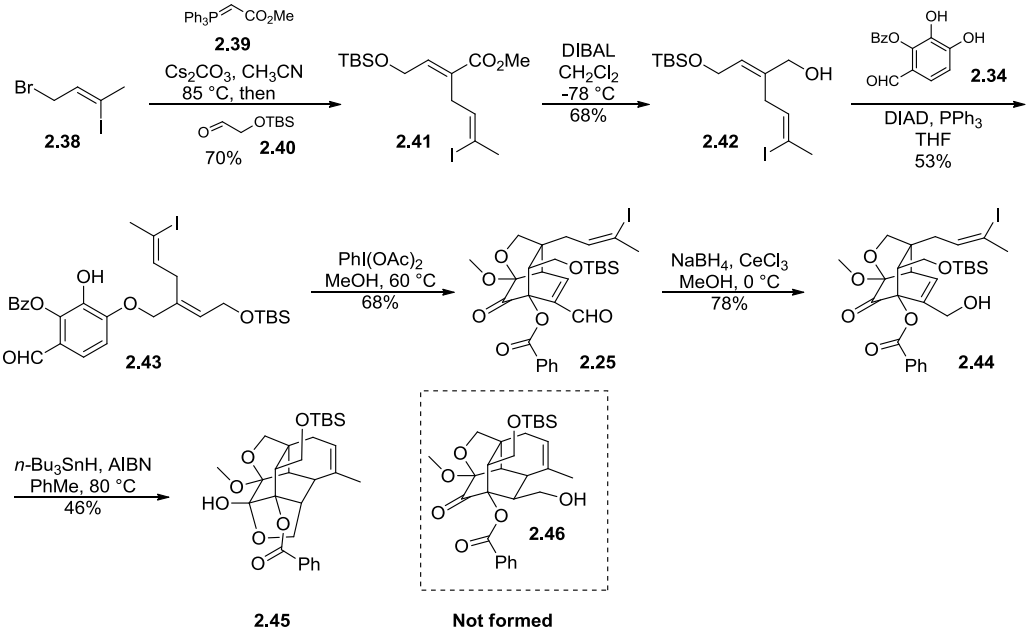
indication of the existence of desired product **2.37** was detected. The results suggested that the radical cyclization did occur. However, when the resultant radical intermediate was quenched, it generated undesired diastereomer of the primary alcohol, which could not serve as a precursor for the desired ring closure. Under the reaction condition, the axial primary alcohol attacked the adjacent ketone and formed hemiacetal **2.35**. The second pathway that the radical intermediate underwent was 1,6-hydrogen abstraction, as it had been observed in the previous route, and subsequent 6-*exo* cyclization to generate **2.36**.



Scheme 2.6. Back-to-Front Stepwise Radical Cyclization

In parallel with the synthesis of **2.22**, the synthesis of substrate **2.25** was also pursued. Unlike in the previous route, diene **2.41** was generated by Wittig coupling of allylic bromide **2.38**, phosphorane **2.39** and aldehyde **2.40**. Then following a same synthetic sequence of DIBAL reduction, Mitsunobu coupling, OD/IMDA and Luche reduction, alcohol **2.44** was obtained. Unfortunately the same result was observed

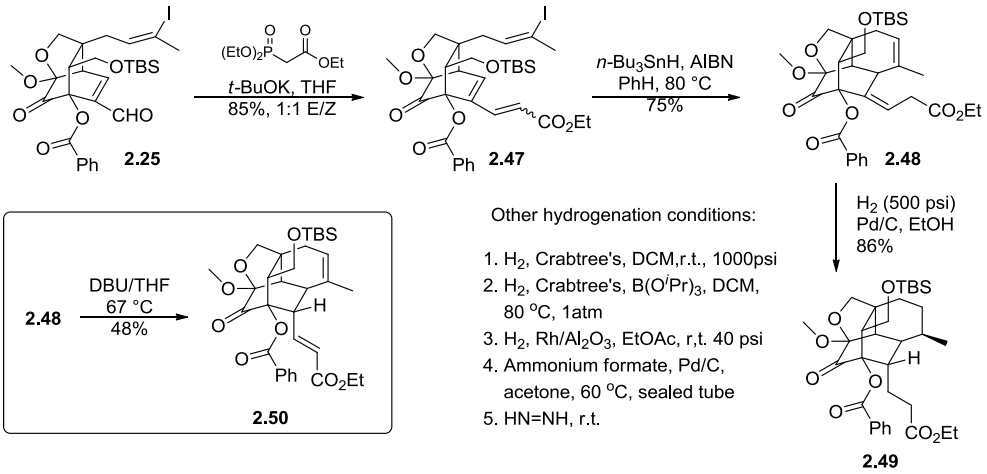
when **2.44** was treated with tributyltin hydride and AIBN, affording the undesired product **2.45**. Clearly, in these two radical routes (Scheme 2.6 and 2.7), contrary to expectation and unlike for **1.72**, the hydrogen radical trapped from the more steric hindered, *convex*, face of the rigid bicyclic carbon skeleton. This stereochemical outcome could possibly be rationalized by the thermodynamically *unfavorable* configuration of the desired diastereomers (**2.37** and **2.46**).



Scheme 2.7. 2nd Back-to-Front Stepwise Radical Cyclization

It was postulated that this problem could be alleviated by first homologating aldehyde **2.25** prior to radical cyclization, in hopes that the resultant tricyclic olefin could be reduced favorably. This idea inspired the synthesis of **2.47** as shown in Scheme 2.8. As expected, the desired *tri*-substituted olefin was efficiently afforded by radical cyclization (**2.48**). However, all the attempts at hydrogenation produced the undesired diastereomer (**2.49**), despite extensive testing of different conditions.

Further efforts to isomerize the *tri*-substituted olefin **2.48** to set stereochemistry correctly by DBU also proved to be unsuccessful (**2.50**).



Scheme 2.8. Stepwise Radical Cyclization of Conjugated Ester

2.3 Conclusion

It was further demonstrated that strategic application of OD/IMDA reaction, followed by cyclization could be utilized to construct the vinigrol skeleton. However, the radical cyclizations suffered from either unwanted hydrogen abstraction or unfavorable diastereoselectivity. The prospect of overcoming this problem seemed daunting, and for that reason a revised synthetic strategy was developed.

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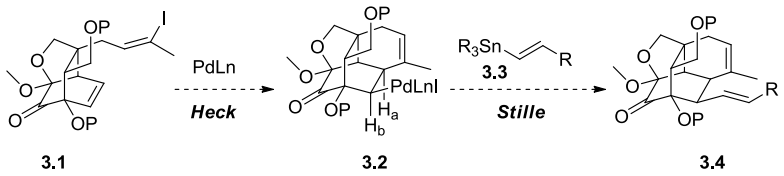
Chapter 3

Synthesis of the Vinigrol Core Using Palladium Chemistry

3.1 Heck-Stille Cascade

3.1.1 Synthetic Strategy

In the previous chapter, attempts to construct the vinigrol core using radical cyclization reactions did not afford the desired tricyclic products. For the radical substrates (aldehyde series) that did cyclize as planned, the radical unfortunately terminated to afford stereochemistry that precluded a second cyclization. It was postulated that this problem could be circumvented by employing a palladium catalyzed cyclization strategy using similar substrates (Scheme 3.1). Palladium chemistry became appealing because of its stereospecific *syn* addition. It was postulated that upon reaction of vinyl iodide **3.1** with palladium, the intermediate would undergo a favorable 6-*exo*-*trig* cyclization to form **3.2**. C-Pd σ bond in **3.2** is *anti* to H_a and *syn* elimination becomes impossible, not to mention that a severely strained cage would prohibit C-C bond rotation. The newly formed palladium intermediate could then transmetalate with an active organometallic species, such as organostannane (**3.3**) to form a new C-C bond with the desired *syn*-stereochemisty (**3.4**).

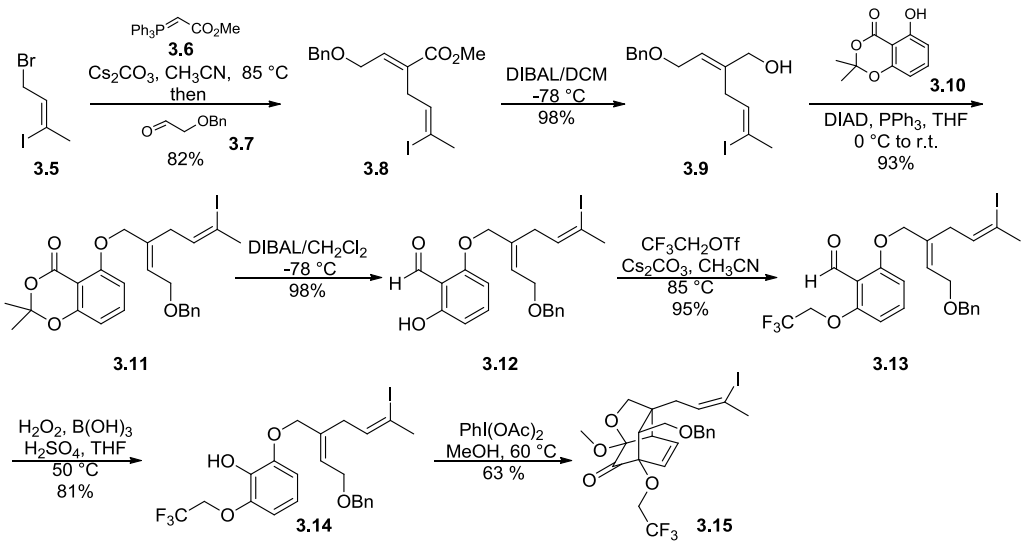


Scheme 3.1. Proposed Palladium Chemistry

3.1.2 Results and Discussion

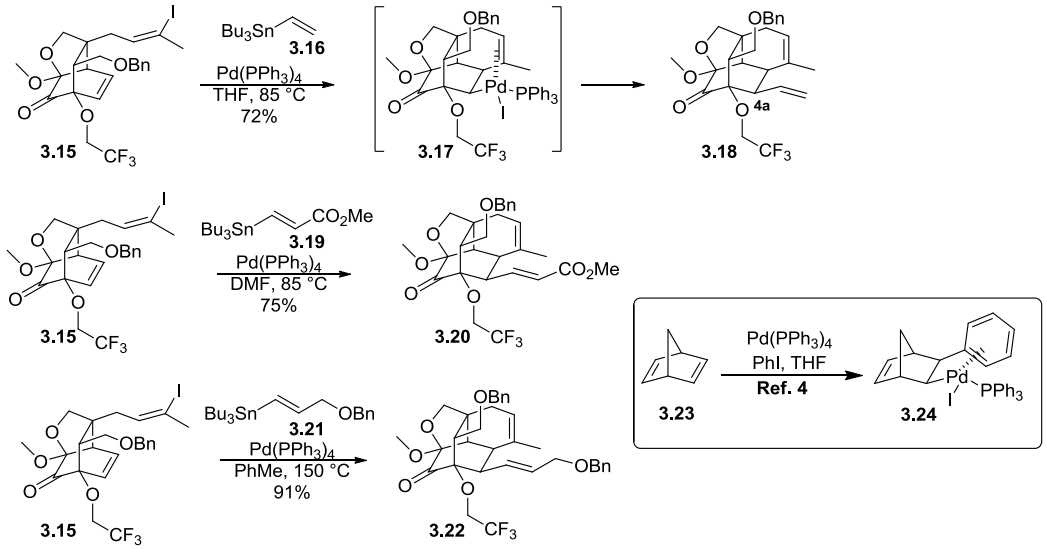
In order to investigate this idea, an oxidative dearomatization/intramolecular Diels-Alder (OD/IMDA) approach was employed to access cyclization precursor **3.1** (Scheme 3.2). Wittig olefination between aldehyde **3.7**[1] and *in situ* formed

phosphorane provided ester **3.8**, which was reduced to allylic alcohol **3.9**. After Mitsunobu reaction with phenol **3.10**,[2] acetonide **3.11** was reduced to benzylaldehyde **3.12**. The phenolic hydroxyl group was then protected as a *β,β,β*-trifluoroethyl ether (**3.13**) and the benzylaldehyde was converted to phenol (**3.14**) by a Dakin oxidation process.[3] The OD/IMDA reaction proceeded smoothly using previously described reaction conditions to deliver **3.15**, which set the stage for the key palladium reaction. The unusual trifluoroethyl group was selected as a protecting group to satisfy the electronic requirements of the Dakin oxidation and OD/IMDA reaction. It is well understood that the Dakin oxidation works best if the aromatic aldehyde is electron rich. In addition, early experimentations had demonstrated that an electron-withdrawing group was necessary to control the regioselectivity in the oxidative dearomatization reaction.[4] Compared with other protecting groups, such as methyl, benzyl and tosyl groups, the trifluoroethyl group poses a fine balance between these two seemingly contradictory electronic demands.



Scheme 3.2. Synthesis of the Heck-Stille Reaction Precursor

To test the critical Heck-Stille cascade reaction, a mixture of vinyl iodide **3.15** and tributyl(vinyl)tin in THF was heated to 85 °C in the presence of palladium catalyst (Scheme 3.3). Gratifyingly, the reaction proceeded successfully and, more importantly, set the stereochemistry at C4a correctly, which was verified by NOESY (Figure 3.1). Furthermore, the palladium-π complex intermediate **3.17** was also isolated and its structure was established by 2D-NMR and ^{31}P-NMR. In fact, a similar palladium-π complex **3.24** had been reported in the literature.[5] Encouraged by this result, two more compounds (**3.20**, **3.22**) were also synthesized using different organostannane coupling partners.



Scheme 3.3. Successful Palladium Cascade

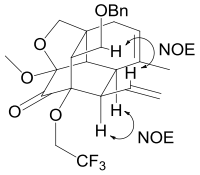
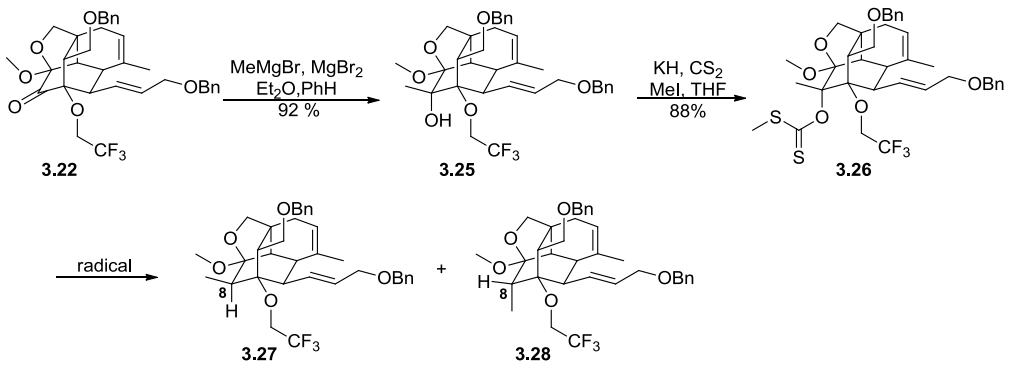


Figure 3.1. NOE Correlations of **3.18**

It was reported by Hanna's group that stereocontrol of the C8 methyl group at late stage of their synthesis was troublesome;[6] therefore, introduction of the C8 methyl group was then pursued at this relatively early stage. First, a radical deoxygenation protocol was attempted (Scheme 3.4).[7] The methyl group was incorporated using a Grignard addition reaction (**3.25**) and the resultant alcohol was converted to a xanthate (**3.26**). To achieve a stereoselective addition of methylmagnesium bromide to ketone **3.22**, different Lewis acid additives ($MgBr_2$ and $CeCl_3$) and solvents (THF and Et_2O) were screened.[8] Eventually, excellent selectivity was obtained by using diethyl ether as solvent in the presence of $MgBr_2$ ($MgBr_2$ was used to assist in solubilizing $MgBr_2$ in ether). Unfortunately, upon treatment of **3.26** with *n*-Bu_3SnH and AIBN, a mixture of two diastereomers **3.27** and **3.28** resulted, with the major one (**3.27**) being the undesired diastereomer. Using milder radical reaction conditions (*n*-Bu_3SnH, Et_3B, O_2, -78 °C) the reaction was more stereoselective, however, again favoring the undesired diastereomer.

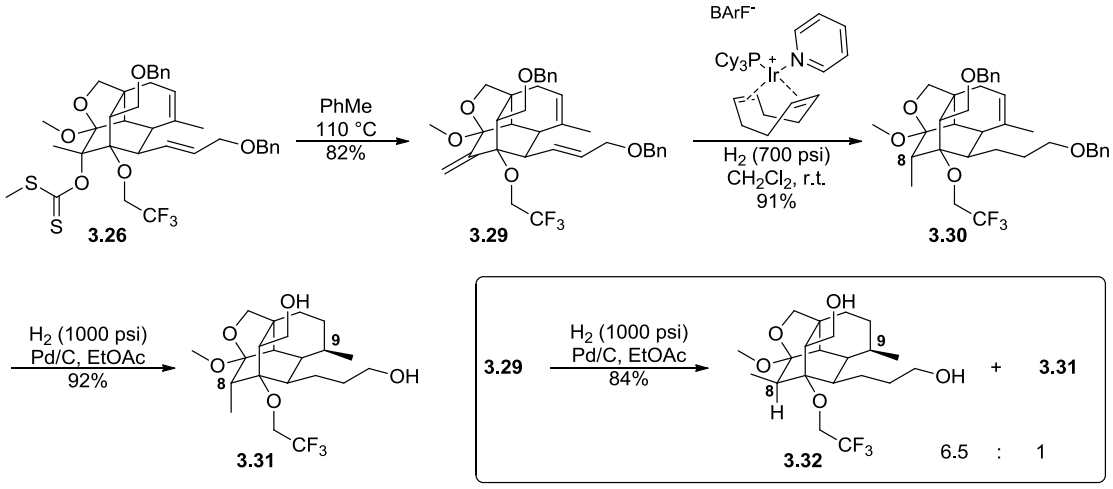


Scheme 3.4. Installation of the C8 Methyl Group – Radical Approach

The high temperature radical reaction conditions (*n*-Bu_3SnH, AIBN, PhMe, 85 °C) generated a trace amount of Chugaev elimination product **3.29**,[9] which presented

us with an opportunity to use an olefin hydrogenation route to install the C8 methyl (Scheme 3.5). It was hoped that the adjacent furan oxygen could serve as a directing group during hydrogenation of the front terminal olefin, and the back *tri*-substituted olefin could also be hydrogenated simultaneously. Toward that end, xanthate **3.26** was heated to reflux in toluene and the olefin was generated in 82% yield. When the olefin was first treated with Pd/C catalyst under 1000 psi of H_2, the reaction afforded a 6.5:1 mixture of two diastereomers, favoring the undesired one (**3.32**). However, we were pleased to find that the back olefin was reduced as predicted in a substrate control manner, to set the C9 methyl correctly. It is noteworthy that high pressure is necessary to reduce this *tri*-substituted olefin.

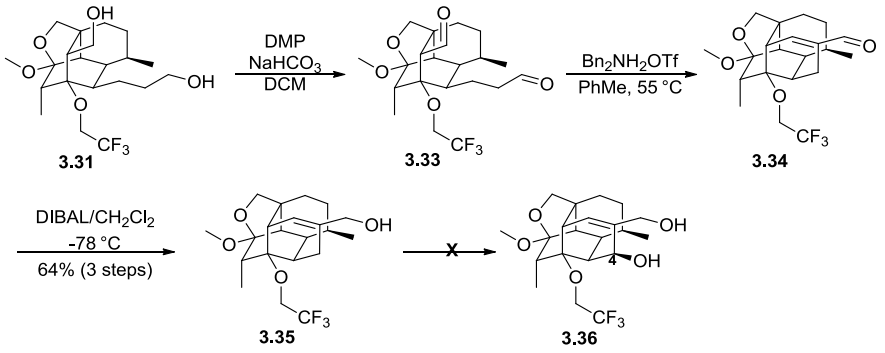
Various heterogeneous and homogeneous hydrogenation conditions were then surveyed. Delightfully, it was found that the front terminal olefin was readily reduced to the desired diastereomer (**3.30**) using Pfaltz's version of Crabtree's catalyst.[10] This complete reversal in selectivity confirmed the coordination of the iridium catalyst to the furanyl oxygen. By following this excellent result with a Pd/C hydrogenation, the installation of C8 and C9 methyl groups was successfully realized in two hydrogenation operations. During the second hydrogenation, the two benzyl groups were also removed to afford diol **3.31**.



Scheme 3.5. Installation of the C8 Methyl Group – Hydrogenation Approach

After the hydrogenation sequence to generate C8 methyl was validated, an effort to shorten the steps of converting **3.22** to **3.29** was initiated. The most sensible solution was direct olefination. Therefore, variety of olefination conditions, including Wittig olefination, Horner-Wadsworth-Emmons olefination, Peterson olefination and olefinations employing Tebbe reagent, Petasis reagent and Nysted reagent[11] were attempted, unfortunately, without success. However, it was found that alcohol **3.25** could be transformed to **3.29** by dehydration under the conditions of $SOCl_2$ in pyridine at room temperature or Burgess's reagent[12] in toluene at 110 °C. Since these conditions were inferior to the xanthate route in terms of yields (33% and 34% respectively), further exploration was therefore discontinued.

Subsequently, intramolecular aldol condensations were evaluated for the closure of the front ring. Delightfully, double oxidation of **3.31** afforded dialdehyde **3.33**, which upon treatment with dibenzylammonium trifluoroacetate[13] at 45 °C for 16 h, cyclized to tetracyclic cage **3.34**. This aldol condensation product was then reduced with DIBAL to furnish **3.35**.

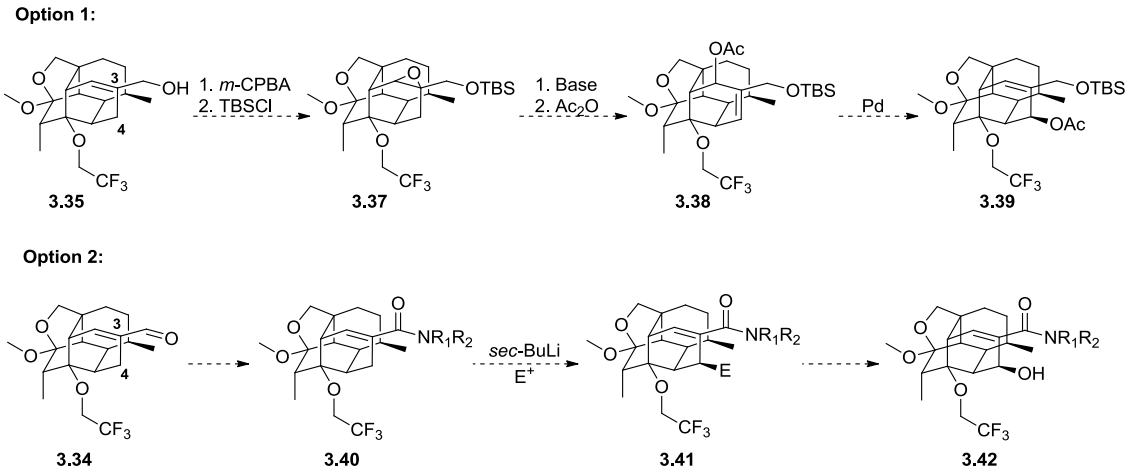


Scheme 3.6. Synthesis of the Tetracyclic Core

At this point, a route to construct the core of vinigrol, based on a Heck-Stille cascade reaction had been developed. With **3.35** in hand, we set out to incorporate the C4 hydroxyl group. Initial screening of a variety of oxidation conditions revealed that the C4 methylene group was quite unreactive toward oxidants (conditions included: SeO_2, dioxane, 100 °C; SeO_2, HCO_2H, dioxane, 60 °C; $C_6F_5SeO_2H$, PhH, 80°C; TPP, O_2, hν, $CHCl_3$).[14] In only a few cases, a reaction occurred, leading to either oxidation of the alcohol to aldehyde or the opening of the back acetal. The lack of reactivity of **3.35** to allylic oxidation can possibly be attributed to the rigid cage structure. Alternatively, the trifluoroethyl group hanging above the core could prevent any enophile (SeO_2 or singlet oxygen) from accessing the alkene during the first step (ene reaction) of allylic oxidation.

Alternative approaches to install the C4 hydroxyl group (Scheme 3.7) were considered. For example, a directed epoxidation on **3.35** could be followed by protection and a base mediated epoxide opening. After acylation (**3.38**), the isomerization could be achieved with palladium catalyst to provide the desired acylated alcohol.[15] Alternatively, the α,β- unsaturated aldehyde could be transformed into an amide. After deprotonation, the resultant anion could be captured with an

electrophile, following the example of Beak, [16] to deliver **3.41**, which could be further elaborated to **3.42**. Although these seemed like reasonable options, we were concerned about the possibility that the steric hindrance of the core structure would not allow any manipulation at C4. We instead chose to follow a strategy that would afford a tetracyclic cage with an olefin in the C3-C4 position, which could enable a more feasible incorporation of a hydroxyl group at C4.



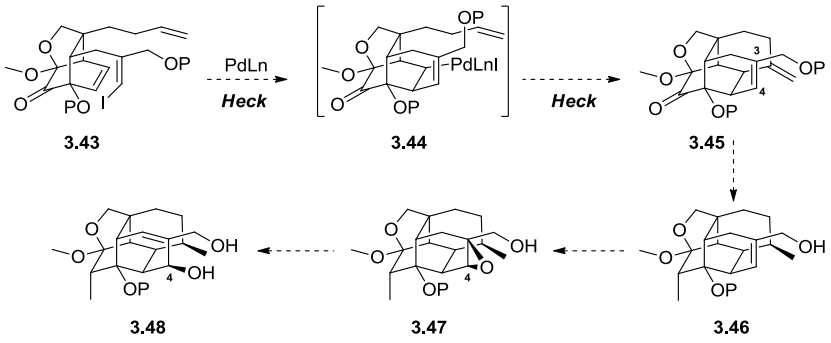
Scheme 3.7. Other Possible Options to Install the C4 Hydroxyl Group

3.2 Tandem Heck Reaction

3.2.1 Synthetic Strategy

Earlier (Chapter 2), it was demonstrated that the vinigrol core could be constructed using either front to back or back to front cyclization approaches. Building on the success of the of Heck-Stille cascade, we decided to explore a front to back approach using tandem Heck chemistry (Scheme 3.8).[17] It was envisioned that after the first palladium insertion to the alkene, the σ-palladium (II) intermediate (**3.44**) would undergo a second intramolecular Heck reaction with the pendant terminal alkene to provide **3.45**. In addition to its conciseness to construct the vinigrol core,

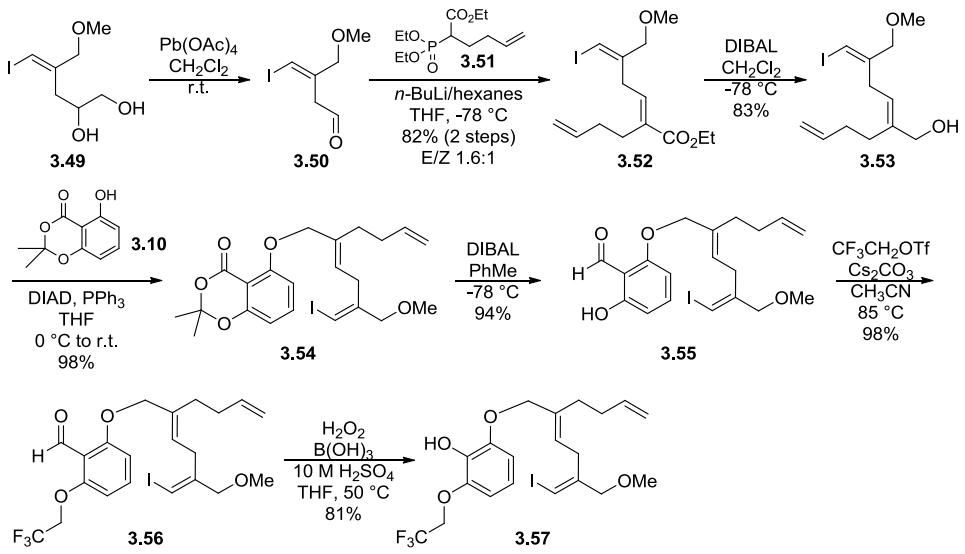
one salient benefit of this approach was that it would generate a C3-C4 olefin, which would allow more attractive manipulations (epoxidation and ring opening) to introduce C4 the hydroxyl group.



Scheme 3.8. Tandem Heck Reaction

3.2.2 Results and Discussion

The preparation of the tandem Heck reaction precursor utilized the same OD/IMDA strategy. The synthesis commenced with a Horner-Wadsworth-Emmons olefination between known phosphonate **3.51**[18] and previously prepared aldehyde **3.50** (Scheme 3.9). This reaction proceeded in good yield but poor *E/Z* selectivity, despite extensive optimization. The *E* isomer (**3.52**) was separated by silica gel column chromatography and reduced to corresponding allylic alcohol (**3.53**), which was coupled with aromatic piece **3.10** to provide **3.54**. As previously, following the reduction of the acetonide, protection with *β,β,β*-trifluoroethyl and Dakin oxidation, **3.57** was ready for the key OD/IMDA reaction.



Scheme 3.9. Synthesis of the OD/IMDA Precursor

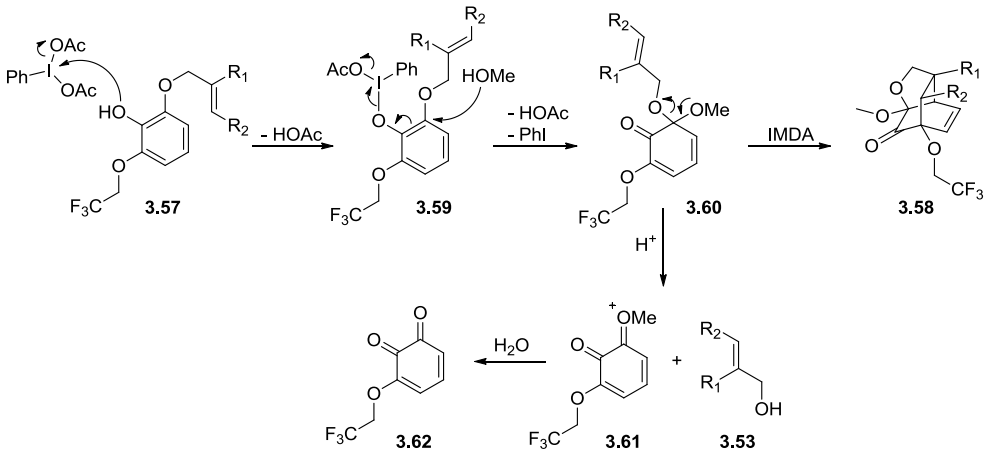
Attempts to apply the same OD/IMDA reaction conditions used before were met with little success, producing the desired product in only 10% yield (Table 3.1, entry 1). Changing the solvent did not make much difference (entry 2, 3). When the reaction was performed at 110 °C, it did not afford any detectable product (entry 4). It was found that the oxidant phenyliodonium diacetate (PIDA) slowly decomposed at high temperature. Using that clue, the oxidative dearomatization was then performed at lower temperatures (-78 °C and -40 °C) and the subsequent intramolecular Diels-Alder was then allowed to proceed at higher temperatures (60 °C, entry 5, 6). These modifications resulted in slightly improved yields. It is well established[19] that trifluoroethanol can be a beneficial solvent for oxidative aromatization reactions, which was also proven true in this case. When trifluoroethanol was used, the reaction yield doubled compared to the first run (entry 7). An inorganic base ($NaHCO_3$) was then added to the reaction in an effort to buffer the reaction (the oxidant releases acid) and suppress unwanted decompositions (entry 8). As shown in Scheme 3.10, the oxidative dearomatization intermediate **3.60** can undergo acetal hydrolysis and extrude

allylic alcohol **3.53** in acidic environment. 2,6-lutidine also worked as efficiently as $NaHCO_3$ (entry 9). Later it was found that before heating the dearomatization product, dilution with more solvent greatly improved the yield, presumably by suppressing self-dimerization of the dearomatization intermediate (entry 10, 11). In a typical procedure, the starting material was dissolved in trifluoroethanol and cooled to -40 °C, 2,6-lutidine was then added, followed by dropwise addition of PIDA (1.05 equivalent). After stirring at -40 °C for 1.0 h, the reaction solution was diluted with trifluoroethanol to the concentration of 0.0025 M. The solution was then heated to 60 °C and stirred for 2 hours. Removal of solvent and 2,6-lutidine *in vacuo* and silica gel column chromatography afforded 64% yield of desired compound.

Table 3.1. OD/IMDA Optimization[a]

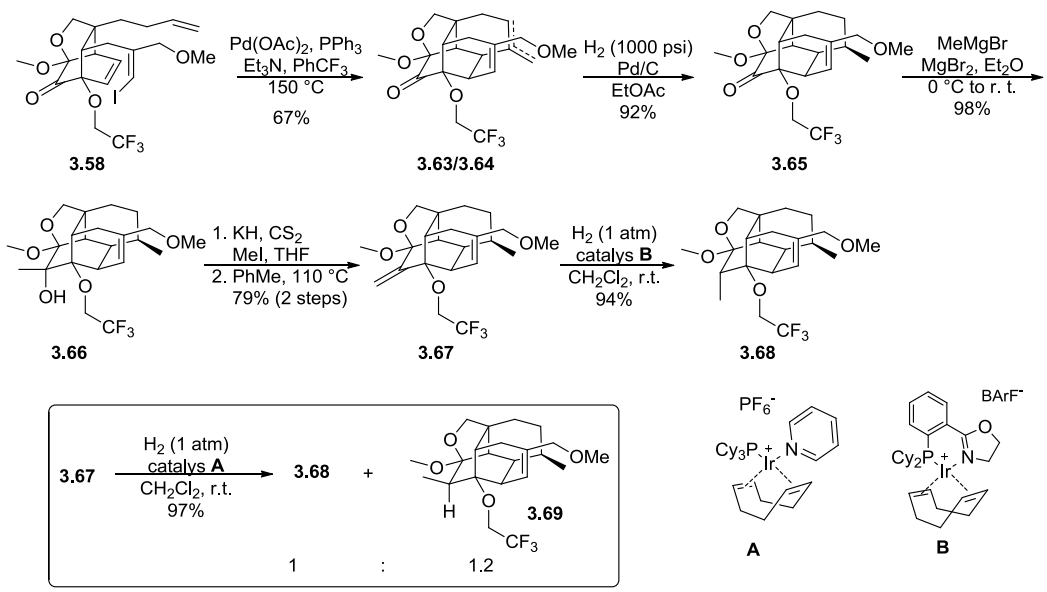
Entry	Solvent	Temp (°C) (addition, stirring)	Base	Time (h) (addition, stirring)	Final concentration(M)	Yield (%)
1	MeOH	60, 60	-	2.5, 4.0	0.01	10
2	DCM	60, 60	-	2.0, 1.5	0.01	10
3	toluene	60, 60	-	2.5, 4.0	0.01	6
4	toluene	110, 110	-	1.5, 2.0	0.01	0
5	MeOH	-78, 60	-	1.0, 3.0	0.01	15
6	MeOH	-40, 60	-	1.0, 2.0	0.01	15
7	CF_3CH_2OH	-40, 60	-	1.0, 2.0	0.01	21
8	CF_3CH_2OH	-40, 60	$NaHCO_3$	1.0, 2.0	0.01	30
9	CF_3CH_2OH	-40, 60	2,6-lutidine	1.0, 2.0	0.01	35
10	CF_3CH_2OH	-40, 60	2,6-lutidine	1.0, 2.0	0.005	53
11	CF_3CH_2OH[b]	-40, 60	2,6-lutidine	1.0, 2.0	0.0025	64

[a] Starting material was dissolved in the solvent (0.01 M), base was added, if applied, then PIDA in MeOH was added over indicated period of time at indicated temperature, the reaction was diluted with same solvent, if applied, then warmed to higher temperature and stirred for indicated period of time. [b] For large-scale batches, the reaction was diluted with toluene, and as a result, the yield slightly decreased.



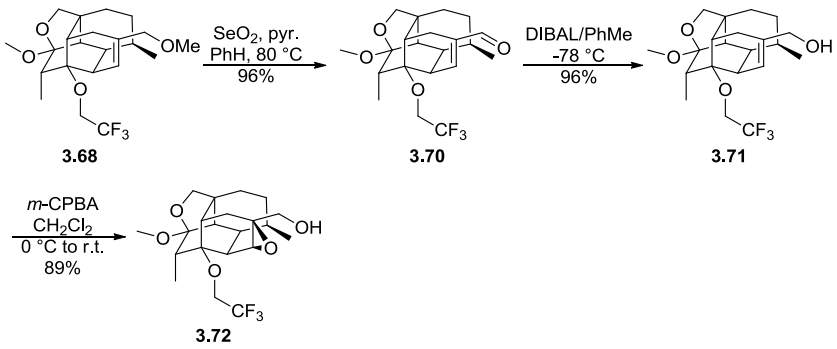
Scheme 3.10. Acid-mediated Decomposition Pathway of **3.57** during OD

The subsequent tandem Heck reaction, employing catalytic palladium(II) acetate, triphenylphospine and triethylamine in trifluorotoluene at 150 °C, proceeded smoothly, furnishing a 5:1 mixture of *exo/endo* products (**3.63/3.64**, Scheme 3.11). Choosing trifluorotoluene as solvent was beneficial as far as the *exo/endo* ratio is concerned. This solvent greatly accelerated the reaction rate, which result in less *exo* olefin being isomerized to the *endo* olefin. However this isomerization did not become an issue since both products were readily reduced to **3.65**. After hydrogenation, the front ketone was converted to an alkene using the Chugaev elimination protocol (**3.67**) as before. Exposure of the alkene to hydrogen in the presence of Crabtree's catalyst resulted in a 1.2:1 mixture of two diastereomers; remarkably, by changing the catalyst to Pfaltz's catalyst,[10] the hydrogenation proceeded with excellent stereocontrol, favoring the desired diastereomer.



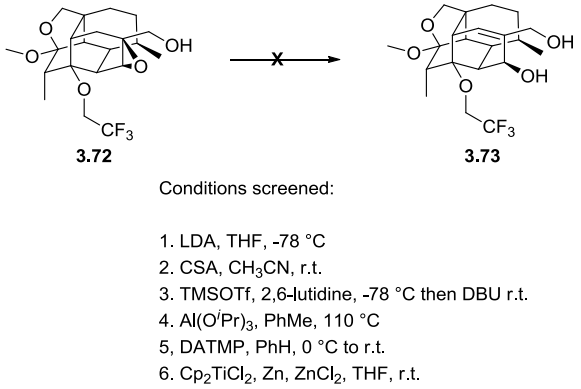
Scheme 3.11. Synthesis of the Tetracyclic Core – Tandem Heck Route

With **3.68** in hand, attention was then directed to the installation of the C4-hydroxyl group (Scheme 3.12). Removal of methyl ether was achieved by a selenium dioxide oxidation (**3.70**)[20] and subsequent reduction of the aldehyde. When the resultant allylic alcohol (**3.71**) was treated with *meta*-chloroperoxybenzoic acid, one single product (**3.72**) was isolated by silica gel column chromatography. Although without definitive proof of the stereochemistry of product **3.72**, complete facial selectivity of the directed epoxidation was expected, since the oxygen could only be delivered from outside the cage.



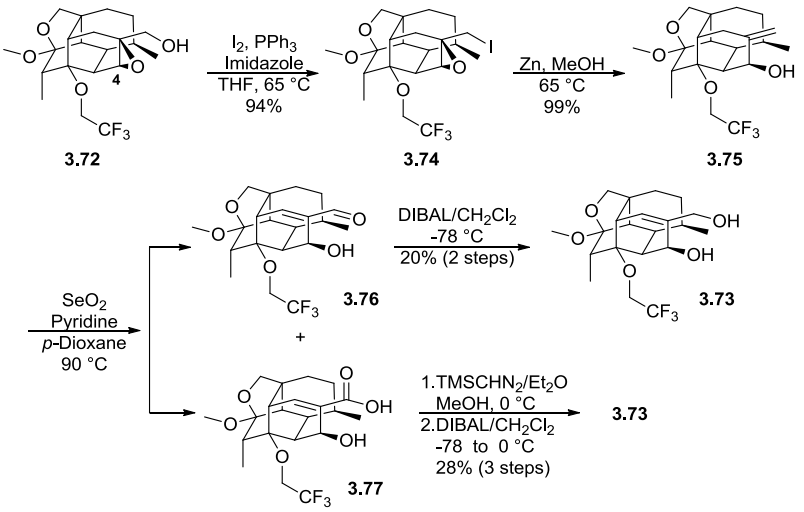
Scheme 3.12. Directed Epoxidation

However, attempts to open epoxide **3.72** with bases or Lewis acids[21] proved to be fruitless, leading to either unreacted starting material, decomposition of starting material or reductive cleavage of the epoxide, which again reflected the steric hindrance of the tetracyclic core of vinigrol (Scheme 3.13).



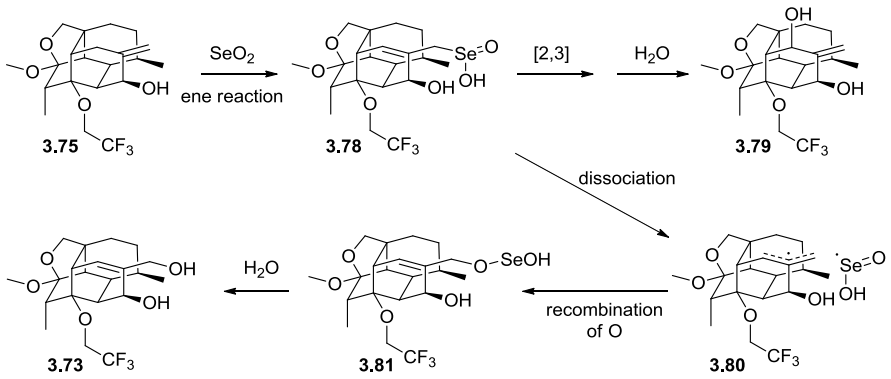
Scheme 3.13. Failed Epoxide Opening Attempts

Eventually, this problem was solved by adapting an exocyclic reductive ring-opening strategy (Scheme 3.14). Alcohol **3.72** was transformed to an iodide (**3.74**), which was exposed to zinc powder upon heating in methanol to generate **3.75**.[22] Isomerization and oxidation of the exocyclic olefin was accomplished under heating with selenium dioxide in *p*-dioxane, furnishing aldehyde **3.76** and **3.77**, which were all reduced to alcohol **3.73**.



Scheme 3.14. Installation of the C4 Hydroxyl Group

The reaction proceeded presumably through an ene reaction and subsequent dissociation-recombination pathway (Scheme 3.15). Exocyclic olefin **3.75** was very responsive to the action of SeO_2. Simple stirring **3.75** with SeO_2 in CH_2Cl_2 for 2 h at r.t. produced a lower R_f spot on TLC plate (0.05 in 80% ethyl acetate/hexanes). Although no definitive characterization was taken on this intermediate, it is very likely to be seleninic acid **3.78**. As proposed by Sharpless,[23] this intermediate can undergo homolytic dissociation to form a radical pair **3.80** under thermal conditions. If recombination occurs at oxygen, **3.81** forms and produces **3.73** after hydrolysis. This high energy dissociation-recombination route could compete with the typical [2,3] sigmatropic rearrangement only because of the unfavorable steric interaction in the transition state of [2,3] sigmatropic rearrangement, which is especially true in this case.



Scheme 3.15. Possible SeO_2 Reaction Pathway

3.3 Conclusion

Two routes based on palladium cascade reactions have been explored to construct the vinigrol core. In both routes, the C9 methyl was set using substrate control while the C8 methyl was set using catalyst control. The tandem Heck reaction route enables us to incorporate the C4 hydroxyl group with correct stereochemistry. The final challenges that needed to be addressed were: 1) fragmentation of the core; 2) installation of isopropyl group; and 3) deprotection of the trifluoroethyl group.

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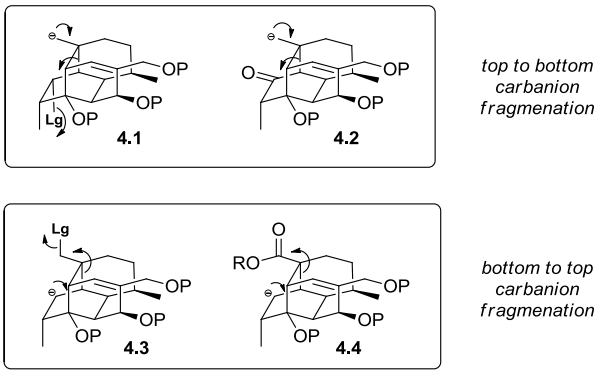
Chapter 4

Completion of the Synthesis of Vinigrol

4.1 Fragmentation

4.1.1 Synthetic Strategies

Having achieved a route to the core of vinigrol, we set out to tackle the task of opening up the tetracyclic cage via fragmentation. Two types of fragmentations appeared most tempting to us: a SmI_2 mediated fragmentation (Scheme 4.1, **4.2**, **4.4**)[1] and a Grob type fragmentation (**4.1**, **4.3**)[2]. In both cases, we envisioned that the fragmentation could be initiated by a carbanion or a ketyl radical from either the top or the bottom of the tetracyclic cage.



Scheme 4.1. Fragmentation Options

SmI_2, as a one-electron donor, can be used in both one- and two-electron processes; it is remarkably selective and therefore tolerant of a variety of generally labile functional groups.[3] Transformations carried out using SmI_2 are often performed at low temperatures. The prospect of using this mild reagent was quite attractive, particularly at a late stage of the synthesis.

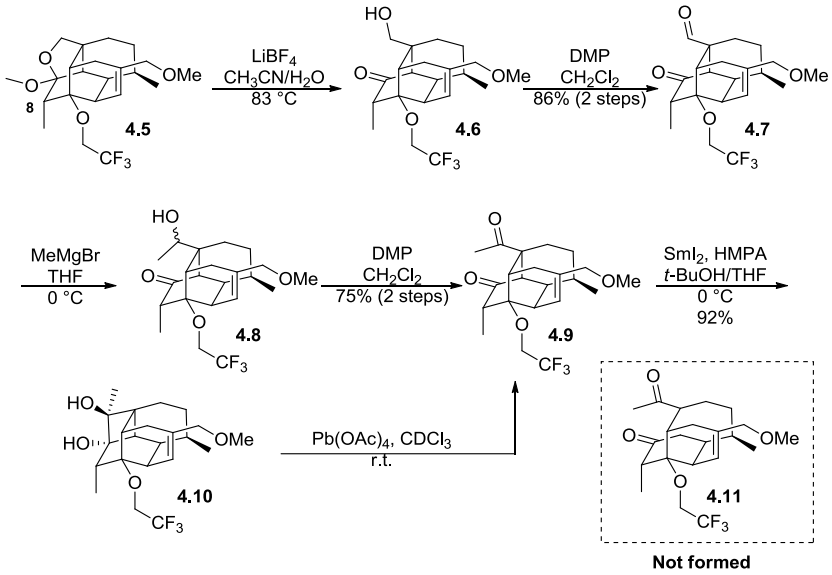
Although the most common form of SmI_2 mediated C-C cleavage is that of strained ring systems, especially cyclopropane and cyclobutane systems, and examples of greater ring systems or no-strain systems are rare in the literature,[4] it was believed

that, in the case of vinigrol, the fragmentation is feasible, due to the potential of releasing great strain energy in the tetracyclic cage.

4.1.2 Results and Discussion

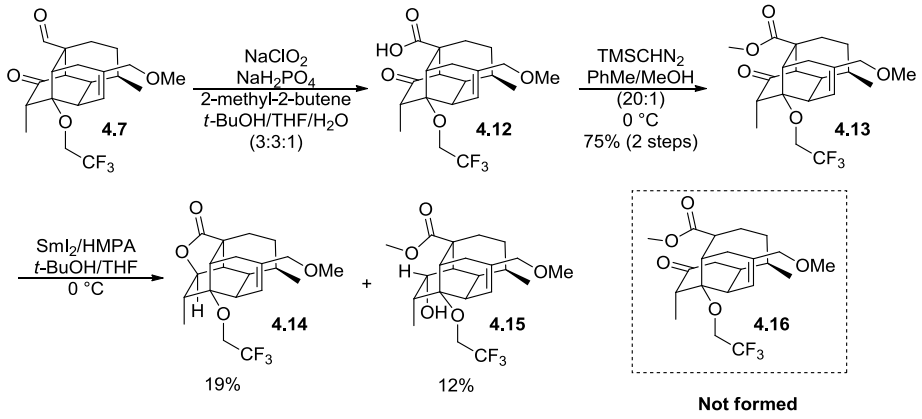
An easily accessible fragmentation substrate **4.9** was prepared (Scheme 4.2). Careful opening of the back acetal, without epimerization of the adjacent C8 stereocenter, was accomplished by $LiBF_4$ in acetonitrile and water.[5] The resultant alcohol **4.6** was then oxidized to aldehyde **4.7**. After Grignard addition and oxidation, diketone **4.9** was obtained in good yield.

Surprisingly, when **4.9** was subjected to reaction condition, reported to be successful for 1,4-diketone fragmentations (SmI_2 and HMPA in *t*-BuOH and THF), the expected C-C fragmentation did not occur, instead pinacol coupling product **4.10** was the only product isolated. In addition to the convincing 2D-NMR characterization data, the identification of this product was further confirmed when it was treated with lead (IV) acetate and clearly reversed to **4.9**. It was reported that the presence of HMPA in the reaction could prevent or slow the chelate formation via the two carbonyl moieties onto the SmI_2, required for C-C bond formation in such pinacol-type reactions, thereby favoring the fragmentation pathway (the presence of HMPA does enhance the rate of reaction of SmI_2 with carbonyl moieties).[6] This reaction outcome could only be explained by the lower activation energy induced by the great proximity between two ketones, compensating the increase in strain of an already strained [2.2.2] system after pinacol formation.



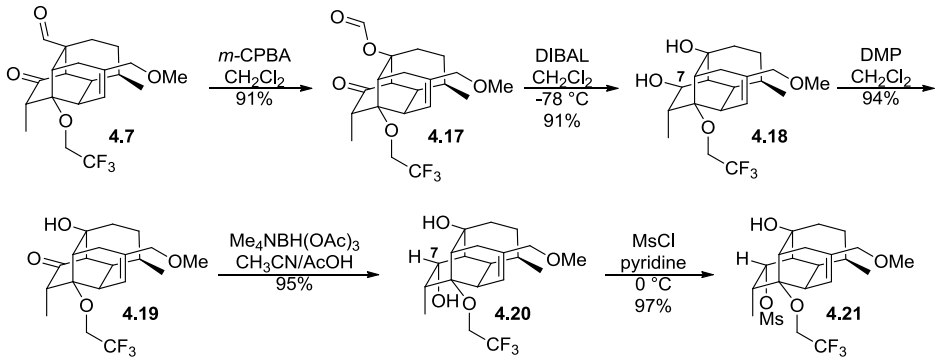
Scheme 4.2. SmI_2 Mediated Diketone Fragmentation Attempt

Alternatively, another fragmentation substrate (**4.13)** was investigated, wherein the pinacol pathway was expected to be less favored. Ketone-ester **4.13** was synthesized in two steps from **4.7** employing a Pinnick oxidation, followed by an esterification. However, **4.13** also failed to afford any fragmentation product. Instead, two products lactone **4.14** and alcohol **4.15** were isolated.



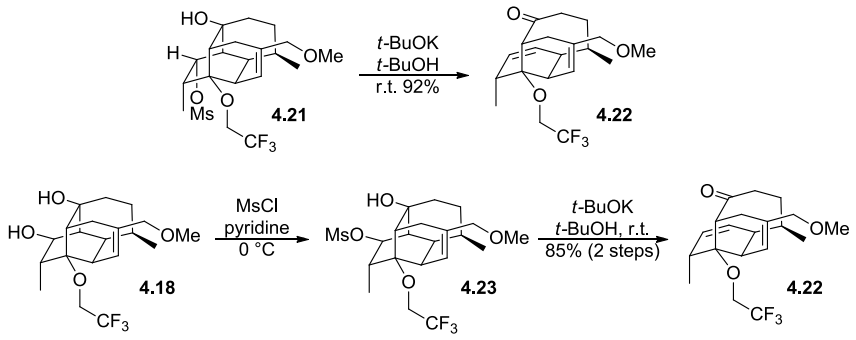
Scheme 4.3. SmI_2 Mediated Ketone-ester Fragmentation Attempt

The unsuccessful attempts of SmI_2 meditated fragmentation prompted investigation into a more reliable Wharton fragmentation strategy, wherein compound **4.21** would be the target of synthesis. As shown in Scheme 4.4, dialdehyde **4.7** underwent a selective Baeyer-Villiger oxidation, affording formate ester **4.17** in excellent yield. In line with previous experiments, the front olefin was found to be inert under the reaction conditions. Subsequent DIBAL reduction then furnished 1,3-diol **4.18**. Although diol **4.18** is potentially competent for fragmentation, the orbitals of the C7-epimer would be better aligned; therefore the C7 stereocenter was inverted by oxidation of the secondary alcohol (**4.18**), followed by a diastereoselective Evans-Saksena reduction (**4.20**).[7] Derivatization of the secondary alcohol as a mesylate (**4.21**) was then readily performed using methanesulfonyl chloride in pyridine.



Scheme 4.4. Synthesis of the Wharton Fragmentation Precursor

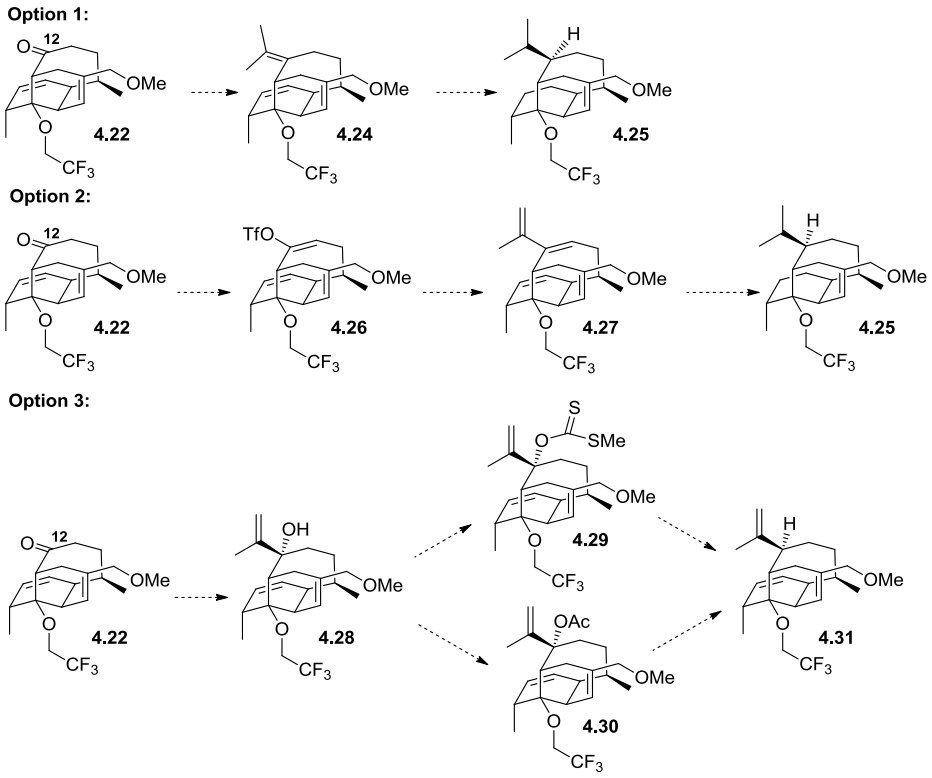
Gratifyingly, when **4.21** was treated with potassium *tert*-butoxide in *tert*-butanol, **4.22** was obtained in excellent yield (Scheme 4.5). Although the stereoelectronic all-*anti* arrangement is the general prerequisite for Grob-type fragmentations, there are a number of examples in the literature of *syn* and *anti* fragmentations showing similar reactivity.[8] To explore this possibility, **4.23** was prepared from **4.18** and treated under the same reaction conditions. The reaction did occur, and efficiently produced the same product **4.22**. It is interesting to note the difference in behavior between the two mesylates. Mesylate **4.23** was formed much faster than its epimer **4.21** due to less steric crowding (3 hours *vs*. 15 hours employing the same reaction conditions: 10 eq. MsCl in pyridine, 0 °C), while its fragmentation was much slower as expected (15 h *vs.* 1.5 h, same reaction conditions: 3 eq. *t*-BuOK in *t*-BuOH, r.t.).



Scheme 4.5. Wharton Fragmentation

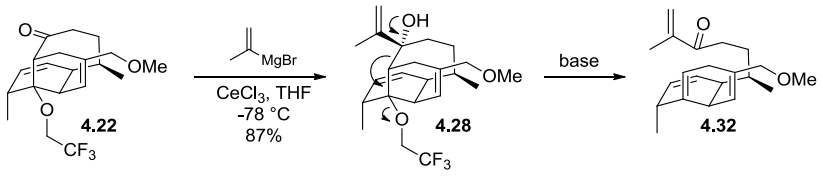
4.2 Installation of the Isopropyl Group

At this stage, after an efficient synthesis for the tricyclic core of vinigrol had been developed, the installation of the isopropyl group at C12 carbonyl seemed readily within reach, considering the well precedented approaches to address the similar tasks in the literature.[9] Several options to install the isopropyl group are shown in Scheme 4.6. However, it was soon discovered that option 1 was hampered by the impossibility of performing a Wittig condensation to form olefin **4.24**. Following a brief exploration of option 2, it was also discontinued due to the inability of generating triflate **4.26**. Our attention therefore turned to the third option. It was envisioned that tricyclic alcohol **4.28**, derived from addition of isopropenylmagnesium bromide to ketone **4.22**, could be elaborated into **4.29** or **4.30** using standard xanthate formation or acylation conditions. Exposure of xanthate **4.29** to radical conditions would afford the desired isopropenyl product **4.31**. In the case of allylic acetate **4.30**, it could undergo a transition metal catalyzed reductive coupling to afford **4.31**. Low level calculations (molecular mechanics) and modeling of vinigrol had revealed that C12 isopropyl group is positioned in a more thermodynamically stable position, therefore the desired stereochemistry should be accessed under thermodynamic conditions.



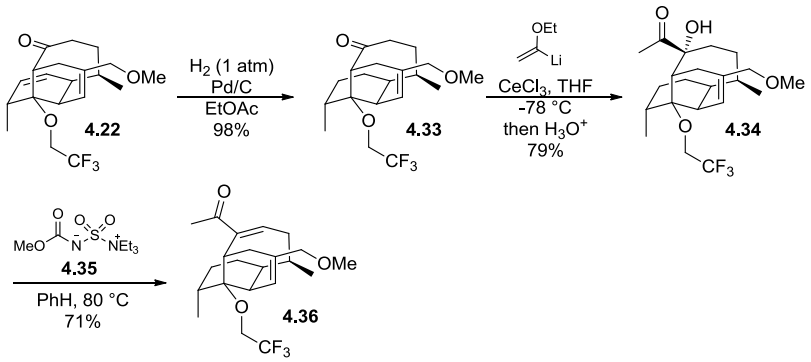
Scheme 4.6. Options for Installing the C12 Isopropyl Group

As expected, the addition of isopropenylmagnesium bromide proceeded smoothly with the aid of cerium chloride,[10] affording **4.28** as a single diastereomer (Scheme 4.7). When **4.28** was treated with potassium hydride followed by carbon disulfide and iodomethane, interestingly, a major product was isolated and proved to be undesired fragmentation product **4.32** by ^{1}H-NMR analysis. Similarly, attempts to form acetate **4.30** using milder bases, such as triethylamine and pyridine, also suffered from the same issue of producing **4.32**. It appeared that the alkoxide underwent a Grob fragmentation easily due to its propensity to release strain energy. This is the first reported example of a Grob fragmentation wherein a trifluoroethyl ether serves the role of a leaving group.



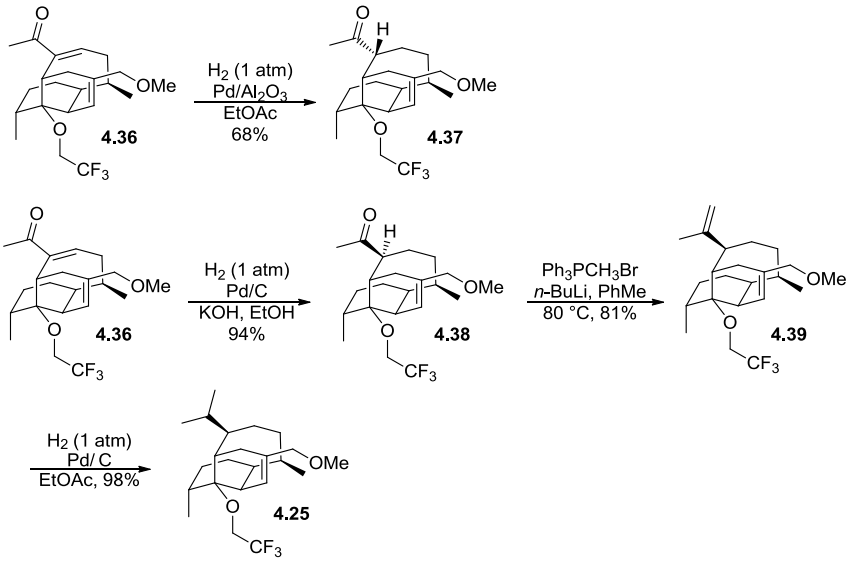
Scheme 4.7. Unwanted Grob Fragmentation

At this point, reaction conditions to navigate around this surprisingly facile fragmentation were highly desirable. Fortunately, it was discovered that after hydrogenation, compound **4.28** could be dehydrated to two regioisomers with Burgess's reagent.[11] Although these two compounds were not advanced due to the low yield of the reaction and their resistance to further hydrogenation, this promising preliminary result promoted us to devise a new approach to install the isopropyl group (Scheme 4.8). Following hydrogenation, 1-ethoxyvinyllithium was added to the ketone **4.33**. The resultant enol ether was then carefully hydrolyzed to α-hydroxy ketone **4.34**. Gratifyingly, Burgess dehydration afforded α,β-unsaturated ketone **4.36**. Although the efficiency of this reaction was modest, the Burgess dehydration enabled us to circumvent the troublesome Grob fragmentation pathway. Furthermore, the resultant α,β-unsaturated ketone presented us with a perfect opportunity of precise stereo-control of its reduction.

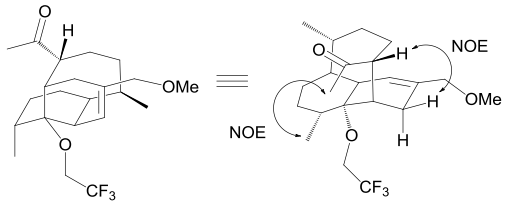


Scheme 4.8. Formation of α,β-Unsaturated Ketone **4.36**

First attempts to selectively reduce ketone **4.36** with Selectrides[12] led to a mixture of unidentified compounds. Copper hydride reagent (Red-Al, CuBr, -20 °C)[13] generated primarily undesired 1,2-reduction product. Several hydrogenation conditions were then examined. Interestingly, stirring **4.36** with palladium on carbon or alumina under hydrogen atmosphere in ethyl acetate yielded one major product (**4.37**, Scheme 4.9), which was assigned by 2D-NMR as the undesired C12-epimer of the methyl ketone (Figure 4.1). Although it was possible to convert **4.37** to desired epimer by isomerization,[14] this approach appeared not ideal, due to the facts that these hydrogenation conditions also generated some unidentified by-products and the reaction was found to be irreproducible. Although the reason for this was unclear, it was speculated that the slightly acidic surface of the "neutral" catalyst was resulting in the partial decomposition of the vinigrol framework. To alleviate the problems, hydrogenation was then performed in the presence of potassium hydroxide.[15] Delightfully, these alkaline hydrogenation conditions furnished the desired C12-epimer (**4.38**) in excellent yield. Following a Wittig olefination and reduction, the installation of the C12-isopropyl group was then completed (**4.25**).



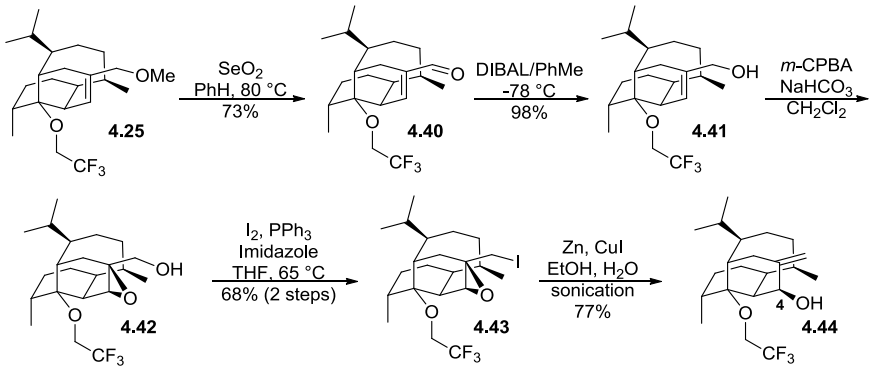
Scheme 4.9. Installation of the C12 Isopropyl Group



Firgure 4.1. NOE Correlations of **4.37**

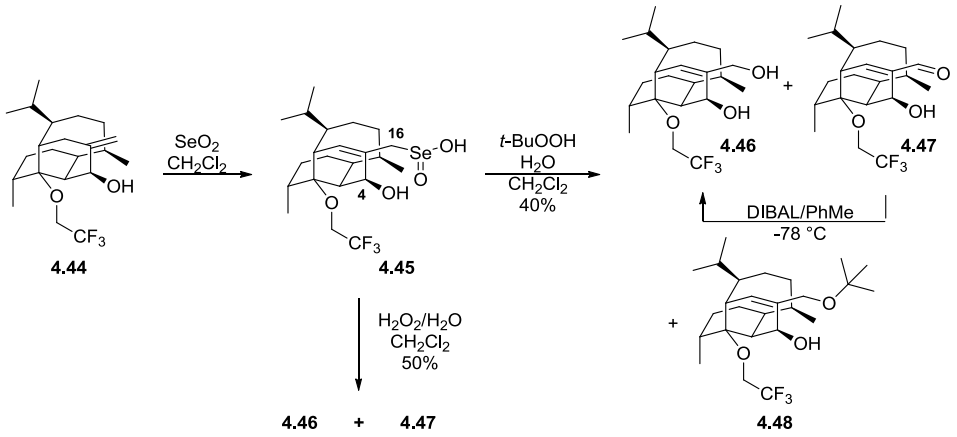
4.3 Installation of the C4 Hydroxyl Group

The same protocol we had developed previously for the C4 hydroxyl installation (Chapter 3, Scheme 3.12, 3.14) was then employed on **4.25** (Scheme 4.10). Thus, following a sequence of methoxy group removal (**4.41**), directed epoxidation of the allylic alcohol (**4.42**), iodination (**4.43**) and reductive ring opening of the epoxide, exocyclic olefin **4.44** was obtained. It was noteworthy that the ring opening of **4.43** proceeded only with the assistance of sonication in this case.[16]



Scheme 4.10. Installation of the C4 Hydroxyl Group

Surprisingly, when **4.44** was exposed to selenium dioxide in refluxing benzene, none of the desired product was detected. A similar intermediate (**4.45)** as observed earlier was seen, judging by ^{1}H-NMR and its low R_f on TLC plate (0.05 in 80% ethyl acetate/hexanes). Conditions to oxidize the C16-selenium group to a primary alcohol were therefore sought. Based on limited literature on this subject, it was suggested that seleninic acids could be oxidized to selenonic acids by sodium periodate[17] or dimethyldioxirane (DMDO)[18] and then displaced by a nucleophile, such as I^- or H_2O. To probe the reactivity of seleninic acid intermediate **4.45**, *tert*-butyl hydropeoxide, a widely used co-oxidant in selenium dioxide oxidation systems,[19] was first chosen as an oxidant (Scheme 4.11). Pleasingly, after stirring **4.45** with *tert*-butyl hydroperoxide in CH_2Cl_2 at room temperature for 16 hours, the desired alcohol **4.46** was detected in the crude ^{1}H-NMR spectrum. Purification of the crude product also revealed small amounts of other by-products, most notably **4.47,** which could be converted to **4.46** by DIBAL reduction, and **4.48**.



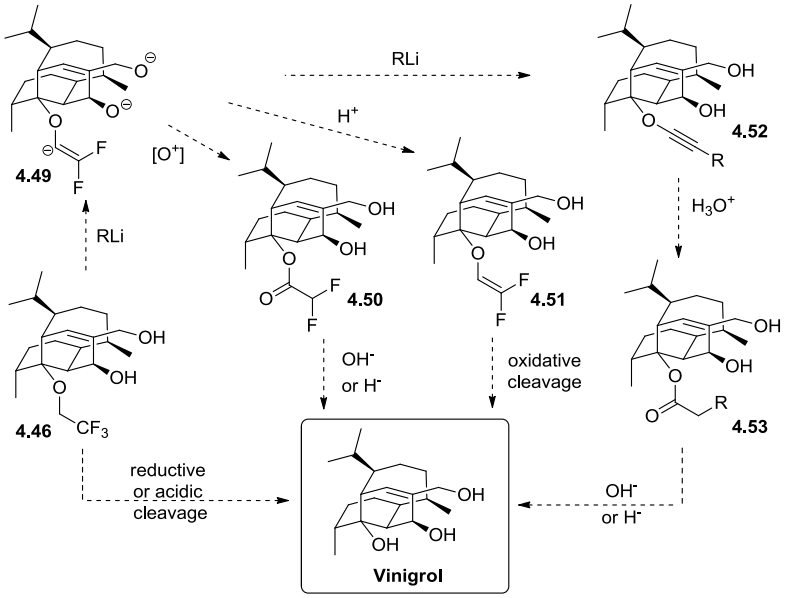
Scheme 4.11. SeO_2 Mediated Isomerization and Oxidation

Alternatively, hydrogen peroxide was also explored as oxidant with expectation that **4.48** should not be generated. Delightfully, the reaction proceeded smoothly, furnishing **4.46** and **4.47**. And most importantly, the front trisubstituted olefin was intact, without epoxidation products being generated.[20]

4.4 Cleavage of the Trifluoroethyl Group

With the installation of the C4-hydroxyl group behind us, the final obstacle of the total synthesis of vinigrol we faced was the cleavage of the trifluoroethyl group. First, it is worth noting that a trifluoroethyl group has never been used as a protecting group in synthesis. With very few scattered examples of this rather stable motif being explored in the literature, deprotection conditions that were compatible with the rest of the vinigrol architecture were sought. It is reported that trifluoroethyl ethers can be converted to base-labile esters by trifluroacetic acid.[21] Vinigrol's susceptibility to acid obviously precluded this harsh approach. A reductive approach using sodium naphthalene as reducing agent only resulted in unreacted starting material. It is also known that trifluoroethyl ethers can be converted to acetylenic esters using

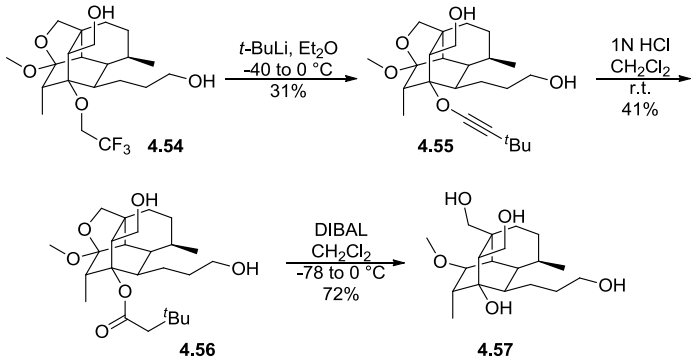
alkyllithium reagents,[22] *via* a difluorovinyllithium intermediate. This is especially interesting to us because in Baran's approach to vinigrol, he demonstrated that vinigrol was compatible with strong bases such as *n*-BuLi.[23] We were curious to learn what product would result if protected vinigrol intermediate **4.46** was submitted to strong bases (Scheme 4.12). If difluorovinyl ether **4.51** was to be obtained, it could potentially be cleaved under oxidative condidtion. If acetylenic ether **4.52** was obtained, this acid vulnerable compound could be converted to ester then cleaved by hydrolysis or reduction to vinigrol. Alternatively, difluorovinyllithium intermediate **4.49**, if long lived enough, could also be trapped with an electrophilic oxygen and converted to vinigrol the same way.



Scheme 4.12. Strategies for Removing Trifluoroethyl Group

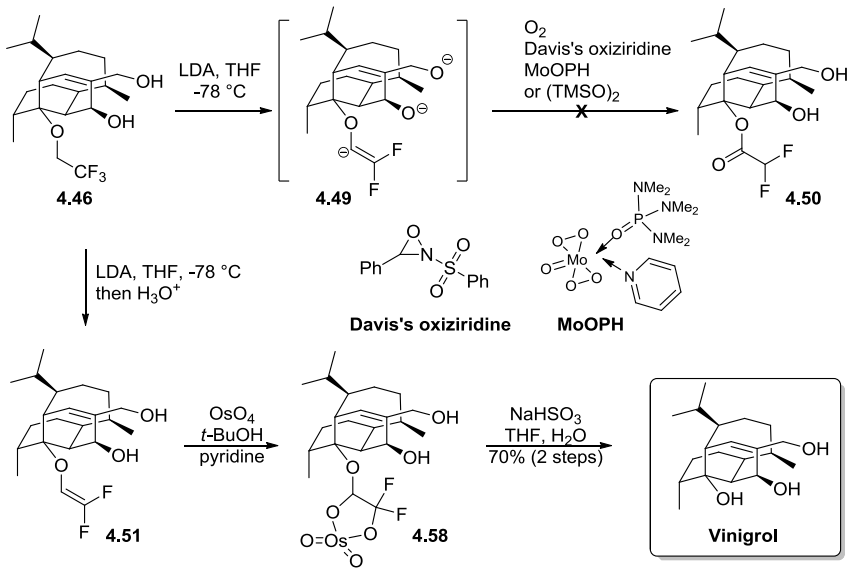
To evaluate the feasibility of these plans, an early intermediate **4.54** was treated with large excess of *tert*-butyl lithium in diethyl ether at -40 °C (Scheme 4.13). To our delight, compound **4.55** was observed, although the yield of the reaction was not ideal (31%). Brief exposure of **4.55** to acid then afforded ester **4.56**, which was

reduced to free alcohol **4.57**. Interestingly, the back acetal was also opened during DIBAL reduction, presumably due to the Lewis acidity of aluminum.



Scheme 4.13. Early Success of Removing Trifluoroethyl Group

Encouraged by this early success in deprotecting the trifluoroethyl group, vinigrol precursor **4.46** was subjected to the same conditions (Scheme 4.14). This time, the reaction proceeded only to the stage of difluorovinyllithium intermediate **4.49**. All attempts to trap this intermediate with electrophilic oxygen reagents, such as molecular oxygen,[24] 2-sulfonyloxaziridine (Davis's oxiziridine),[25] molybdenum peroxide-pyridine-hexamthylphophoramide (MoOPH)[26] and bis(trimethylsilyl)-peroxide (TMSOOTMS)[27] to form difluoroether **4.50** met without success. Eventually, difluorovinyl ether **4.51** was isolated by silica gel column chromatography and oxidized using osmium tetraoxide[28] to form osmate ester **4.58**, which was then hydrolyzed *in situ* during work-up to furnish vinigrol.



Scheme 4.14. Synthesis of Vinigrol- Removal of the Trifluoroethyl Group

4.5 Conclusion

A total synthesis of vinigrol has been accomplished.[29] A key step in this synthesis utilized a strategic oxidative dearomatization/intramolecular Diels-Alder reaction,[30] which coupled with a Heck cyclization cascade, affording the tetracyclic core of vinigrol in only two steps from a simple precursor. The synthesis endeavors feature a number of notable transformations such as: 1) a directed hydrogenation in a very complex and hindered setting, 2) selenium dioxide mediated olefin isomerization and oxidation, 3) Wharton fragmentation, 4) stereoselective installation of an isopropyl group and 5) unique strategic applications and deprotection of trifluoroethyl ethers. Efforts are underway to render the oxidative transformation asymmetric, which would provide access to vinigrol enantiomers.

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APPENDIX 1

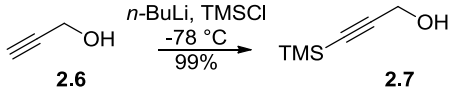
A1.1 General Information

The general information discussed in this section applies to Appendix 2 and 3.

All reactions were performed using flame-dried glassware under an atmosphere of nitrogen with dry solvents, unless otherwise stated. Dry tetrahydrofuran (THF), diethyl ether, dichloromethane (CH_2Cl_2), toluene (PhMe), methanol (MeOH), acetonitrile (CH_3CN) were obtained by passing these previously degassed solvents through activated alumina columns. Benzene (PhH) was distilled from sodium/benzophenone. All other commercial reagents were used as provided. Reactions were monitored by thin layer chromatography (TLC) carried out on EMD silica gel 60-F254 plates. Visualization was performed by UV light irradiation and ceric ammonium molybdate, or anisaldehyde, or potassium permanganate stain and heat. SiliaFlash F60 silica (particle size 40-63μm) was used for flash column chromatography. Preparative thin layer chromatography (prep-TLC) separations were also carried out on EMD silica gel 60-F254 plates. ^{1}H and ^{13}C NMR data was acquired on Varian Inova 400, 500, or 600 (Cornell University) or Bruker DRX 400, 500, or 600 (University of Arizona) spectrometer and the spectra were calibrated using residual solvents as an internal reference ($CDCl_3$: 7.26 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR; C_6D_6: 7.16 ppm for ^{1}H NMR, 128.06 ppm for ^{13}C NMR; CD_3OD: 3.31 ppm for ^{1}H NMR, 49.00 ppm for ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. Infrared spectra were recorded on a

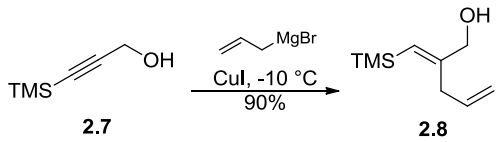
Shimadzu Prestige FT-IR. High resolution mass spectra were acquired at the University of Arizona Mass Spectral Facility.

A1.2 Experimental Procedures for Chapter 2

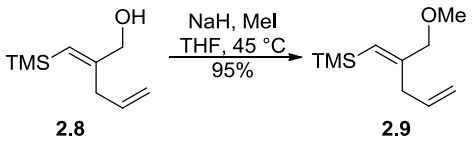


2.6 **2.7**

A solution of propargyl alcohol (12.0 mL, 203.1 mmol) in THF (775 mL) was cooled to -78 °C, and *n*-BuLi (2.5 M in hexanes, 170.6 mL, 426.5 mmol) was added slowly. After stirring for 30 min at -78 °C, trimethylsilyl chloride (57.1 mL, 446.8 mmol) was added dropwise. Once the addition was completed, the cold bath was removed, and the reaction was stirred at r.t. for 2.0 h. The reaction was cooled to 0 °C, quenched by water (100 mL), and then 1 N HCl solution (300 mL) was added to the crude reaction mixture and stirred at r.t. for 1.5h. The complete consumption of the TMS ether was observed by TLC (R_f 0.90 in 10% ethyl acetate/hexanes). The reaction mixture was poured into a separatory funnel, the organic layer was separated and the aqueous layer was extracted with diethyl ether (4 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Purification by vacuum distillation (15 mtor, 50 °C) provided the desired alcohol (25.9 g, 99%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (d, J = 6.1 Hz, 2H), 1.53 (t, J = 6.1 Hz, 1H), 0.18 (s, 9H). The spectrum data is consistent with the reported literature data.[1]

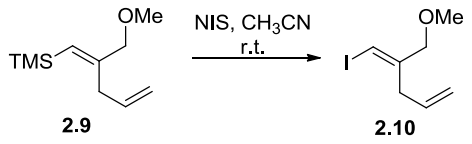


A mixture of 3-(trimethylsilyl)prop-2-ynol (11.9 g, 93.0 mmol), diethyl ether (200 mL), and copper iodide (1.92 g, 10.1 mmol) was stirred and cooled at -10 °C (salt/ice bath) and freshly prepared allylmagnesium bromide (0.085M, 300 mL) was added slowly via cannula. The reaction mixture turned from grey to brown to black over time. After the addition was completed, the reaction was warmed to r.t. naturally and stirred for 12 h totally. The reaction mixture was cooled to 0 °C and quenched by saturated NH_4Cl solution (100 mL) and diluted with water (300 mL). After phase separation, the aqueous phase was filtered through a Celite pad to remove the precipitate. The solution was then extracted with diethyl ether (3 × 150 mL). All organic phases were combined and washed with brine (200 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was distilled under vacuum (15 mtor, 72-73 °C) to afford a light yellow oil (14.2 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.77 (ddt, *J* = 17.1, 10.1, 6.5 Hz, 1H), 5.62 (t, *J* = 1.6 Hz, 1H), 5.08 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.04 (dq, *J* = 10.1, 1.5 Hz, 1H), 4.06 (dd, *J* = 6.2, 1.5 Hz, 2H), 2.93 (dt, *J* = 6.5, 1.6 Hz, 2H), 1.57 (t, *J* = 6.2 Hz, 1H), 0.14 (s, 9H). The spectrum data is consistent with the reported literature data.[2]



2.8 **2.9**

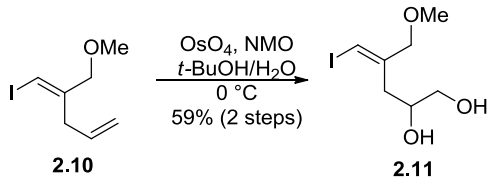
To a suspension of NaH (60 wt%, 5.36 g, 133.9 mmol) and iodomethane (25.1 mL, 401.9 mmol) in THF (160 mL), alcohol (15.2 g, 89.3 mmol) in THF (20 mL) was added dropwise. The reaction mixture was then stirred at 45 °C for 16 h. After that period of time, the starting material was still present by TLC analysis. More NaH (3.56 g, 89.3 mmol) and iodomethane (5.6 mL, 89.3 mmol) were added and stirring continued for 5.0 h. The reaction was cooled to 0 °C and quenched by saturated NH_4Cl solution (50 mL) and diluted with water (50 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 80 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated. Purification by column chromatography (5% diethyl ether/pentane) afforded a light yellow oil (15.6 g, 95%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77 (ddt, J = 17.1, 10.1, 6.5 Hz, 1H), 5.61 (t, J = 1.5 Hz, 1H), 5.07 (dq, J = 17.1, 1.7 Hz, 1H), 5.03 (dq, J = 10.1, 1.5 Hz, 1H), 3.83 (d, J = 1.4 Hz, 1H), 3.33 (s, 3H), 2.90 (dt, J = 6.5, 1.5 Hz, 1H), 0.13 (s, 9H). The spectrum data is consistent with the reported literature data.[2]



2.9 **2.10**

To the solution of TMS-diene (12.1 g, 65.6 mmol) in acetonitrile (230 mL) was added *N*-Iodosuccinimide (17.1g, 76.0 mmol) in portions at 0 °C. After 40 min at

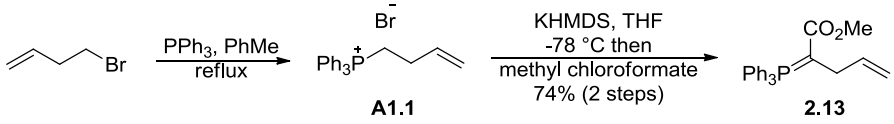
0 °C, the reaction mixture was warmed to r.t., covered with aluminum foil and stirred for 40 h. After that period of time, the reaction was quenched by 10% $Na_2S_2O_3$ solution (200 mL). Two phases were separated and the aqueous phase was extracted with pentane (3 × 150 mL) and the organic phase was also extracted with pentane (6 × 200 mL). The combined extracts were washed with brine (200 mL), dried over anhydrous Na_2SO_4 and carefully concentrated on rotovap. The crude product with residual pentane was used in next step without any further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (tt, *J* = 1.4, 0.5 Hz, 1 H), 5.75 (ddt, *J* = 17.1, 10.0, 6.6 Hz, 1 H), 5.15 (dq, *J* = 17.1, 1.6 Hz, 1 H), 5.09 (ddt, *J* = 10.0, 1.8, 1.3 Hz, 1 H), 3.91 (d, *J* = 1.4 Hz, 2 H), 3.30 (s, 3 H), 2.98 (dt, *J* = 6.6, 1.5 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.11, 133.26, 117.06, 79.49, 74.80, 58.12, 39.43; IR (film) 3059, 2980, 2928, 2926, 2820, 1639, 1211, 1095, 993, 916, 781 cm^{-1} ; HRMS (EI) *m/z* calcd. for $C_7H_{11}IO$ $[M]^+$: 237.9855, found: 237.9861.



2.10 **2.11**

N-Methylmorpholine *N*-oxide monohydrate (9.34 g, 69.1 mmol) was dissolved in water (140 mL) and cooled to 0 °C, and iododiene from the previous step dissolved in *tert*-butanol (140 mL) was added, followed by a solution of osmium tetroxide (2.5 wt%, 12.0 mL, 1.73 mmol) in *tert*-butanol. The reaction was stirred at 0 °C for 8 h then quenched by 15% $NaHSO_3$ solution (250 mL) and extracted with ethyl acetate (6 × 200 mL). The combined extracts were washed with brine (2 × 200 mL), dried over

anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (60% ethyl acetate/hexanes) to afford a light brown oil (10.5 g, 59% yield over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.49 (td, *J* = 1.1, 0.7 Hz, 1H), 4.00 (d, *J* = 1.1 Hz, 2H), 3.93 (ddtd, *J* = 8.8, 6.5, 3.8, 3.3 Hz, 1H), 3.70 (ddd, *J* = 11.2, 6.8, 3.3 Hz, 1H), 3.61 (d, *J* = 3.9 Hz, 1H), 3.53 (ddd, *J* = 11.2, 6.5, 5.4 Hz, 1H), 3.37 (s, 3H), 2.69 (dd, *J* = 6.8, 5.4 Hz, 1H), 2.51 (ddd, *J* = 13.9, 3.9, 0.7 Hz, 1H), 2.40 (dd, *J* = 13.9, 8.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.17, 83.47, 76.70, 70.57, 66.63, 58.28, 39.84; IR (film) 3358, 2926, 2885, 2821, 1610, 1192, 1087, 1033, 910, 783 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_7H_{13}INaO_3$ $[M+Na]^+$: 294.9802, found: 294.9807.

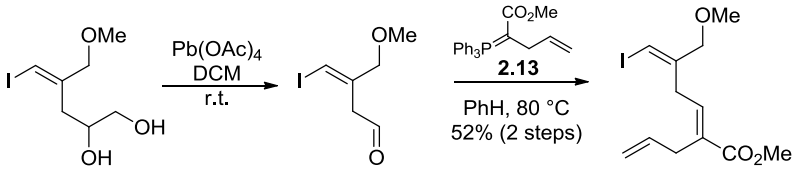


Compound *** was prepared according to literature protocol.[3]

A mixture of 4-bromo-1-butene (5.4 mL, 52.7 mmol) and triphenylphosphine (10.6 g, 40.5 mmol) in toluene (150 mL) was heated at reflux for 24 h. The reaction mixture was then cooled to r.t. and filtered over a Buchner funnel. A white solid was collected, which was washed with toluene (2 × 35 mL) then dried under high vacuum to afford desired product **A1.1** (16.0 g, quantitative yield).

To a solution of phosphonium salt (500 mg, 1.25 mmol) in THF (7.0 mL) was added potassium bis(trimethylsilyl)amide (1.0 M in THF, 5.0 mL) dropwise at -78 °C. After stirring for 1.0 h, methyl chloroformate (0.48 mL, 6.25 mmol) was added. The

reaction mixture was stirred at the same temperature for 30 min. then warmed to r.t. and stirred for 1.0 h. The reaction was quenched by saturated $NaHCO_3$ and diluted with dichloromethane. The organic phase was separated and the aqueous phase was extracted with dichloromethane three times. The combined organic phases were dried over anhydrous $MgSO_4$, filtered and concentrated. The crude product was purified by column chromatography (15% ethanol/ethyl acetate) to afford an off-white solid (348 mg, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 – 7.40 (m, 15H), 5.82 (ddt, *J* = 17.0, 10.0, 6.0 Hz, 1H), 4.67 (ddt, *J* = 10.0, 2.6, 1.4 Hz, 1H), 4.56 (dq, *J* = 17.0, 1.7 Hz, 1H), 3.33 (s, 3H), 2.69 (ddt, *J* = 18.6, 6.0, 1.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.52, 140.93, 133.42 (d, *J* = 9.7 Hz, 6C), 131.48 (d, *J* = 2.8 Hz, 3C), 128.26 (d, *J* = 12.0 Hz, 6C), 127.61 (d, *J* = 90.4 Hz, 3C), 111.65, 49.17, 37.43 (d, *J* = 122.0 Hz), 31.14; IR (film) 3057, 2941, 1627, 1600, 1435, 1323, 1159, 1101, 746, 715, 692, 569, 516 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{24}H_{24}O_2P$ $[M+H]^+$: 375.1508, found: 375.1505.

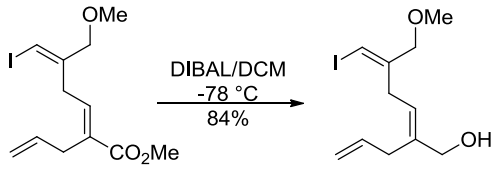


2.11 2.12 2.14

To an ice-water cooled solution of diol (82.0 mg, 0.301 mmol) in CH_2Cl_2 (3.0 mL) was added lead (IV) acetate (155 mg, 0.332 mmol) in one portion. After the addition was completed, the reaction mixture was allowed to warm to r.t. and stirred for 1.0 h. The mixture was poured directly over a silica gel pad, filtered and the filter cake was washed with ethyl acetate. After the filtrate was concentrated on rotovap, the

residue was taken up in diethyl ether and filtered through a Celite pad and washed with ether. The filtrate was concentrated again on rotovap and then placed under high vacuum briefly to remove the residual solvents and formaldehyde. The resultant aldehyde crude product was used immediately.

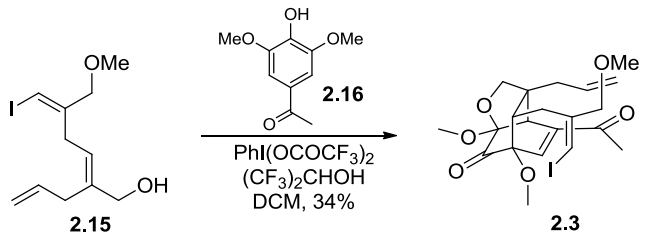
A mixture of phosphorane (281 mg, 0.753 mmol) and the aforementioned aldehyde in benzene (3.0 mL) was placed in a high-pressure tube, capped and heated at 80 °C for 1.0 h. The reaction mixture was cooled to r.t. and concentrated. The residue was purified by column chromatography (10 % ethyl acetate/hexanes) to afford a colorless oil (53.0 mg, 52% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (t, *J* = 7.5 Hz, 1H), 6.41 (s, 1H), 5.84 (ddt, *J* = 17.2, 10.1, 6.1 Hz, 1H), 5.12 – 4.98 (m, 2H), 3.89 (d, *J* = 1.3 Hz, 2H), 3.74 (s, 2H), 3.30 (s, 3H), 3.18 (dt, *J* = 6.1, 1.7 Hz, 2H), 3.15 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.73, 145.54, 138.44, 135.08, 131.85, 115.59, 80.67, 75.05, 58.15, 52.02, 34.71, 31.20; IR (film) 2949, 2926, 1712, 1435, 1276, 1205, 1132, 1093, 914, 783, 765 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{12}H_{18}IO_3$ $[M+H]^+$: 337.0295, found: 337.0292.



2.14 **2.15**

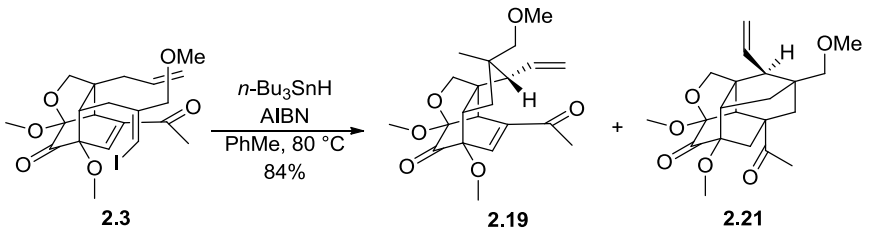
To a solution of ester (455 mg, 1.35 mmol) in dichloromethane (14.0 mL) cooled at -78 °C, DIBAL (1.0 M in CH_2Cl_2, 2.98 mL, 2.98 mmol) was added dropwise. After stirring at -78 °C for 3 h the reaction was quenched by 10% Rochelle's

salt (4.0 mL) and warmed to r.t. The mixture was partitioned between ethyl acetate (25 mL) and Rochelle' salt solution (25 mL) and vigorously stirred for 2 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. After filtration and concentration, the residue was purified by column chromatography (30% ethyl acetate/hexanes) to afford a light yellow oil (349 mg, 84% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, *J* = 1.4, 0.6 Hz, 1H), 5.80 (ddt, *J* = 17.1, 10.0, 6.4 Hz, 1H), 5.45 (dddt, *J* = 8.1, 7.4, 2.2, 1.1 Hz, 1H), 5.10 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.04 (dq, *J* = 10.0, 1.7 Hz, 1H), 4.07 – 4.02 (m, 2H), 3.89 (d, *J* = 1.4 Hz, 2H), 3.29 (s, 2H), 3.02 (d, *J* = 7.4 Hz, 2H), 2.95 (d, *J* = 6.4 Hz, 2H), 1.68 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.87, 139.07, 135.52, 122.26, 115.94, 79.22, 74.91, 66.72, 58.08, 33.73, 32.84; IR (film) 3404, 2976, 2924, 2821, 1635, 1612, 1450, 1375, 1298, 1284, 1265, 1192, 1087, 995, 914, 777, 673 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{11}H_{17}IO_2Na$ $[M+Na]^+$: 331.0165, found: 331.0163.



To a solution of alcohol (32.0 mg, 0.104 mmol) and phenol (61.2 mg, 0.312 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (5.0 mL) was added at r.t. a solution of phenyliodine bis(trifluoroacetate) (134 mg, 0.312 mmol) in 1,1,1,3,3,3-hexafluoropropan-2-ol (1.0 mL) over 2.0 h via syringe pump. After the addition was

completed, the reaction solution was stirred for further 30 min., then partitioned between ethyl acetate and saturated $NaHCO_3$ solution. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate three times. The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (25% ethyl acetate/hexanes) to provide a light yellow oil (18.0 mg, 34% yeild). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (dd, *J* = 2.2, 1.1 Hz, 1H), 6.31 (t, *J* = 1.1 Hz, 1H), 5.86 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.24 – 5.17 (m, 1H), 5.09 (dq, *J* = 16.9, 1.5 Hz, 1H), 4.09 (d, *J* = 8.2 Hz, 1H), 4.03 (dd, *J* = 3.5, 1.0 Hz, 2H), 4.00 (d, *J* = 2.2 Hz, 1H), 3.86 (d, *J* = 8.2 Hz, 1H), 3.56 (s, 3H), 3.46 (s, 3H), 3.29 (s, 3H), 2.94 (t, *J* = 7.2 Hz, 1H), 2.42 (s, 3H), 2.36 (ddd, *J* = 7.6, 2.7, 1.1 Hz, 2H), 2.21 (dd, *J* = 14.5, 7.6 Hz, 1H), 2.09 (dd, *J* = 14.5, 6.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.60, 194.07, 146.95, 139.83, 139.16, 132.60, 120.39, 99.24, 87.20, 80.82, 77.99, 75.55, 57.94, 53.77, 51.32, 49.24, 45.09, 42.33, 35.72, 33.32, 25.12; IR (film) 2976, 2941, 2893, 1766, 1749, 1674, 1249, 1228, 1192, 1089, 1014, 877 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{28}IO_6$ $[M+H]^+$: 503.0925, found: 503.0916.



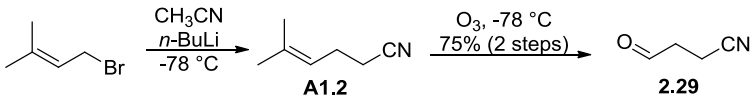
A solution of vinyl iodide (27.0 mg, 0.0538 mmol) in dry toluene (0.80 mL) was heated to 80 °C, to which tributyltin hydride (0.63 M in toluene, 0.10 mL) and

azobisisobutyronitrile (0.11 M in toluene, 0.10 mL) were added simultaneously via syringe pumps over 2.0 h. The reaction was stirred for additional 3.0 h then cooled to r.t. and concentrated. The crude product was purified by column chromatography (25% ethyl acetate/hexanes) to afford two compounds: **2.19** (higher R_f, colorless oil, 9.0 mg, 44% yield) and **2.20** (lower R_f, colorless oil, 8.0 mg, 40% yield).

Compound **2.19**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.99 (t, *J* = 1.7 Hz, 1H), 5.53 (dt, *J* = 16.7, 10.2 Hz, 1H), 5.22 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.13 (dd, *J* = 16.7, 2.0 Hz, 1H), 4.07 (d, *J* = 7.7 Hz, 1H), 3.94 (d, *J* = 2.1 Hz, 1H), 3.88 (d, *J* = 7.7 Hz, 1H), 3.60 (s, 3H), 3.43 (s, 3H), 3.24 (s, 3H), 3.02 (d, *J* = 9.3 Hz, 1H), 2.92 (d, *J* = 9.3 Hz, 1H), 2.88 (m, 1H), 2.39 (s, 3H), 2.05 (d, *J* = 10.2 Hz, 1H), 1.65 (dd, *J* = 13.0, 7.6 Hz, 1H), 1.50 (t, *J* = 12.2 Hz, 1H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, extracted from HSQC and HMBC) δ 198.9, 194.5, 140.9, 138.7, 132.2, 120.7, 98.00, 86.1, 77.9, 76.3, 59.2, 57.2, 53.6, 53.3, 51.1, 47.0, 46.0, 41.5, 37.5, 24.8, 19.5; IR (film) 2954, 2927, 2873, 1759, 1714, 1195, 1109, 1087, 1016, 871.86 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{29}O_6$ $[M+H]^+$: 377.1958, found: 377.1958.

Compound **2.20**: 1H NMR (600 MHz, $CDCl_3$) δ 5.67 (dt, J = 16.8, 10.1 Hz, 1H), 5.20 (dd, J = 16.9, 1.8 Hz, 1H), 5.16 (dd, J = 10.2, 1.8 Hz, 1H), 3.94 (d, J = 8.7 Hz, 1H), 3.67 (d, J = 8.7 Hz, 1H), 3.52 (s, 3H), 3.46 (s, 3H), 3.29 (s, 3H), 3.26 (d, J = 9.3 Hz, 1H), 3.21 (d, J = 9.3 Hz, 1H), 2.79 (d, J = 1.3 Hz, 1H), 2.45 (d, J = 10.1 Hz, 1H), 2.34 (m, 1H), 2.30 (m, 2H), 2.18 (s, 3H), 2.08 (dt, J = 13.9, 1.6 Hz, 1H), 1.88 (ddd, J = 14.1, 10.2, 1.9 Hz, 1H), 1.83 (d, J = 2.7 Hz, 2H); ^{13}C NMR ($CDCl_3$, extracted from HSQC and HMBC) δ 225.0, 208.2, 132.9, 119.4, 103.4, 79.4, 76.7,

72.7, 59.2, 58.8, 52.8, 51.7, 51.3, 49.0, 47.8, 46.9, 45.9, 41.8, 35.0, 31.1, 25.0; IR (film) 2929, 1756, 1706, 1447, 1354, 1198, 1109, 1008 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{29}O_6$ $[M+H]^+$: 377.1958, found: 377.1962.

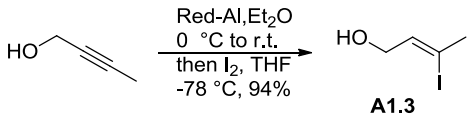


3-cyanopropanal **2.29** was prepared according to literature protocol.[4]

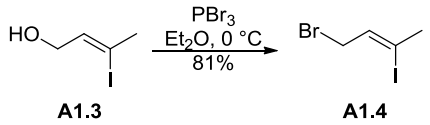
To a solution of acetonitrile (1.0 mL, 20.0 mmol) in THF (50 mL), *n*-BuLi (1.6 M in hexanes, 12.8 mL, 20.5 mmol) was added dropwise at -78 °C while the solution gradually turned to opaque yellow. After stirring for 15 min, 1-bromo-3-methyl-2-butene (2.2 mL, 19.0 mmol) in THF (25 mL) was added dropwise. The reaction mixture was stirred at -78 °C for 4.5 h, then quenched by saturated NH_4Cl solution (30 mL) and warmed to r.t. The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 × 50 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and carefully concentrated in vacuo to afford a light yellow oil. This crude product was used directly in the next step without further purification. ^1H NMR (400 MHz, $CDCl_3$) δ 5.22 – 5.05 (m, 1H), 2.34 (m, 4H), 1.73 (s, 3H), 1.66 (s, 3H).

The crude product from the previous step was dissolved in dichloromethane (80 mL) and purged with ozone at -78 °C until the reaction solution turned blue. The mixture was then purged with N_2 for 15 min and stirred with dimethyl sulfide (5.0 mL) at r.t. for 1.5 h. After evaporation of the solvent, the desired product 3-

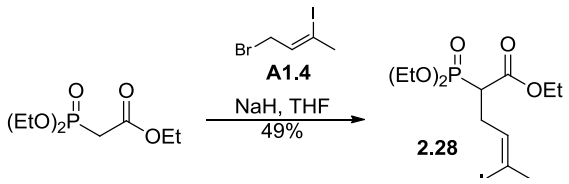
cyanopropanal (1.19 g, 75% yield over 2 steps) was obtained, which was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (s, 1H), 2.92 (t, J = 7.0 Hz, 2H), 2.64 (t, J = 7.0 Hz, 2H).



A solution of Red-Al in toluene (65 wt% in toluene, 150.8 mL, 497.6 mmol) was added dropwise to a stirred solution of 2-butyn-1-ol (15.0 mL, 199.0 mmol) in ethyl ether (720 mL) at 0 °C. The resultant clear solution was warmed to r.t. and stirred for 18 h. After cooling to 0 °C, ethyl acetate (29.2 mL) was added and stirred for 30 min. The solution was cooled to -78 °C and iodine (75.8 g, 298.5 mmol) in THF (250 mL) was added slowly. After the addition was completed, the reaction mixture was allowed to warm to r.t. and stirred for 2 h. The reaction was cooled to 0 °C and saturated $Na_2S_2O_3$ (250 mL) was added. The upper organic phase was decanted and the rest was extracted with ethyl ether (3 × 250 mL). The combined organic phases were washed successively with saturated $Na_2S_2O_3$ (2 × 250 mL), water (250 mL), and brine (250 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The resultant crude product was purified by column chromatography (30% ethyl ether/pentane) to afford a light yellow oil (36.8g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (tq, J = 6.0, 1.5 Hz, 1H), 4.16 (dq, J = 6.0, 1.2 Hz, 2H), 2.53 (dt, J = 1.5, 1.2 Hz; 3H). Spectrum data is consistent with the reported literature data.[5]

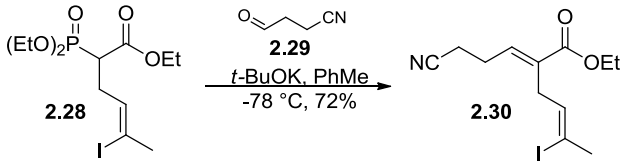


To a solution of allylic alcohol (67.6 g, 270.5 mmol) in ethyl ether (550 mL) was added phosphorus tribromide (12.8 mL, 135.2 mmol) dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h then quenched by brine (100 mL). The organic phase was separated and washed with water (100 mL) and brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The resultant crude product was purified by column chromatography (pure pentane) to afford a colorless oil (57.1 g, 81%), which rapidly turned purple in air. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (tq, *J* = 7.8, 1.6 Hz, 1H), 3.99 (dq, *J* = 7.8, 0.8 Hz, 2H), 2.58 (dt, *J* = 1.6, 0.8 Hz, 3H). Spectrum data is consistent with the reported literature data.[6]



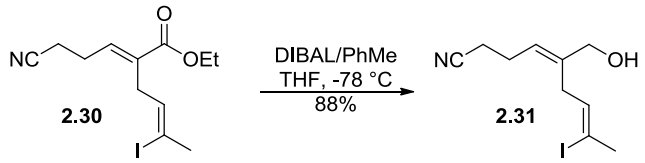
Compound **2.28** was prepared according to literature procedure.[7] To a suspension of NaH (60 wt%, 1.38 g, 34.4 mmol) in THF (60 mL) was added triethyl phosphonoacetate (6.21 mL, 31.3 mmol) dropwise at 0 °C. After stirring for 30 min, (Z)-1-bromo-3-iodo-but-2-ene (8.99 g, 34.4 mmol) was added dropwise at the same temperature. The reaction was allowed to warm up to r.t. and stirred for 4 h then quenched by saturated NH_4Cl solution (20 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined

organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (75% ethyl acetate) to afford a colorless oil (6.23 g, 49% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48 (dddd, J = 6.7, 5.5, 1.9, 0.7 Hz, 1H), 4.28 – 4.10 (m, 6H), 3.04 (ddd, J = 22.3, 10.4, 4.7 Hz, 1H), 2.81 – 2.67 (m, 1H), 2.67 – 2.55 (m, 1H), 2.49 (m, 3H), 1.35 (tdd, J = 7.1, 2.1, 0.6 Hz, 6H), 1.29 (t, J = 7.1 Hz, 3H). The bis-alkylation product was also isolated as a yellow oil (3.66 g, 20% yield).

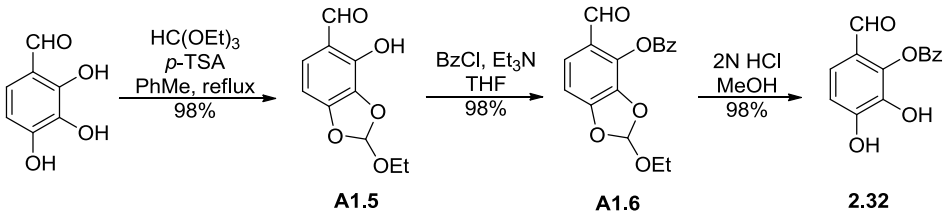


To a solution of phosphonate (2.89 g, 7.16 mmol) in toluene (20 mL), potassium *tert*-butoxide (803.5 mg, 7.16 mmol) was added at 0 °C in portions. After stirring at 0 °C for 30 min, the mixture was cooled to -78 °C and aldehyde (169.5 mg, 2.04 mmol) in toluene (15 mL) was added dropwise. The reaction was stirred at -78 °C for 1.5 h then quenched by saturated NH_4Cl solution (20 mL) and warmed to r.t. The organic phase was separated and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (25% ethyl acetate/hexanes) to afford a light yellow oil (4:1 E/Z mixture, 486.3 mg, 72% yield). The E isomer could be isolated by second column chromatography (10% ethyl acetate/hexanes) and characterized: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (t, J = 7.5 Hz, 1H), 5.45 (tq, J = 6.6, 1.5 Hz, 1H), 4.23 (q, J = 7.1

Hz, 2H), 3.14 (dt, J = 6.6, 1.2 Hz, 2H), 2.65 (q, J = 7.3 Hz, 2H), 2.52 – 2.47 (m, 5H), 1.32 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.80, 138.12, 132.97, 132.37, 118.71, 101.71, 61.16, 35.21, 33.64, 25.13, 16.89, 14.37; IR (film) 2960, 2916, 2247, 1712, 1427, 1282, 1203, 1114, 1093, 1051, 758 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{12}H_{16}INO_2$ $[M]^+$: 333.0226, found: 333.0237.



To a solution of ester (2.35 g, 7.05 mmol) in THF (35 mL) at -78 °C, was added DIBAL (1.2 M in toluene, 12.2 mL, 14.8 mmol) dropwise. The reaction was stirred at -78 °C for 2.5 h and 0 °C for 2 h. After the reaction was diluted with THF (40 mL), water (0.56 mL), 20% NaOH (0.56 mL) and water (1.2 mL) were added in sequence at 0 °C. The mixture was allowed to warm up to r.t. and stirred for 15 min before anhydrous $MgSO_4$ was added. After stirring for another 15 min, the solid was filtered off and washed with diethyl ether. The filtrate was concentrated and purified by column chromatography (50% ethyl acetate/hexanes) to afford a colorless oil (1.60 g, 88% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (tt, J = 7.1, 1.4 Hz, 1H), 5.41 (tq, J = 6.7, 1.5 Hz, 1H), 4.05 (s, 2H), 2.91 (dt, J = 6.7, 1.3 Hz, 2H), 2.51 (q, J = 1.4 Hz, 3H), 2.49 – 2.40 (m, 4H), 2.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.94, 132.32, 122.43, 119.39, 102.33, 66.13, 36.12, 33.54, 23.78, 17.52; IR (film) 3419, 2949, 2914, 2866, 2245, 1423, 1139, 1097, 1074, 1006, 850, 580 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{10}H_{14}INO$ $[M]^+$: 291.0120, found: 291.0111.



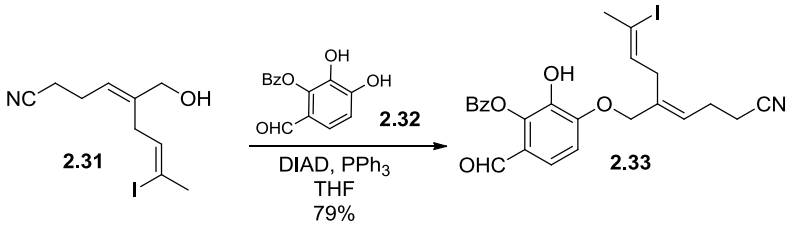
Compound **2.32** was prepared according to literature protocol.[8]

In a 500-mL round-bottom flask equipped with a reflux condenser and a Dean-Stark trap containing 5Å molecular sieves, a mixture of triethylorthoformate (16.7 mL, 100 mmol) and *p*-toluene sulfonic acid (500 mg) in toluene (250 mL) was heated to reflux for 30 min. After the mixture was cooled below refluxing temperature, 2, 3, 4-trihydroxybenzaldehyde (7.71 g, 50 mmol) was added and the mixture was then heated to reflux and stirred for 3 h. The reaction was cooled again and another portion of triethylorthoformate (16.7 mL, 100 mmol) was added and the mixture was refluxed for 16 h. The reaction was cooled to r.t., before cesium carbonate (750 mg) was added, filtered through a Celite pad and washed with toluene (50 mL). The filtrate was concentrated to afford an off-white solid, which was purified by column chromatography (15-20% ethyl acetate/hexanes) to afford a white solid (10.3 g, 98%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 11.05 (s, 1H), 9.75 (s, 1H), 7.19 (d, J = 8.1 Hz, 1H), 6.99 (s, 1H), 6.63 (d, J = 8.1 Hz, 1H), 3.78 (qq, J = 9.4, 7.1 Hz, 2H), 1.29 (t, J = 7.1 Hz, 3H).

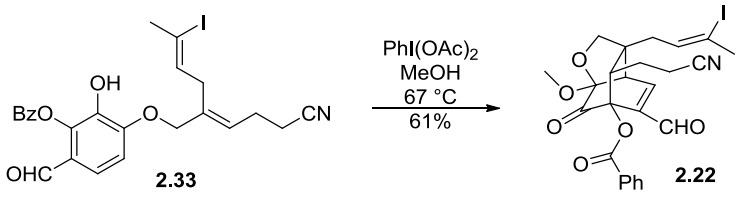
To a solution of phenol (10.3 g, 49.0 mmol) and benzoyl chloride (6.88 mL, 53.9 mmol) in THF (240 mL) was added triethylamine (10.2 mL, 73.5 mmol) dropwise at 0 °C. A white precipitate formed immediately upon addition. The reaction

was warmed to r.t. and stirred for 30 min. After that period of time, the reaction mixture was diluted with ethyl acetate and washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford a white solid (15.1 g, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.30 – 8.19 (m, 2H), 7.73 – 7.63 (m, 1H), 7.59 – 7.50 (m, 3H), 7.03 (s, 1H), 6.94 (d, *J* = 8.2 Hz, 1H), 3.77 (qq, *J* = 9.4, 7.1 Hz, 2H), 1.28 (t, *J* = 7.1 Hz, 3H).

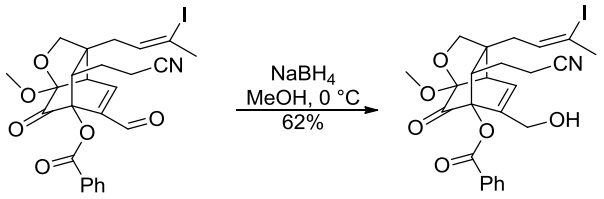
A solution of orthoester (0.27 g, 0.86 mmol) in MeOH/H_2O (2:1 v/v, 8.6 mL) was treated with 2N HCl (16.0 mL, 4.30 mmol) at r.t. for 1 h. The reaction was then concentrated on rotovap. The residue was taken up in ethyl acetate (30 mL) and washed with water (2 × 20 mL) and brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (50 % ethyl acetate/hexanes) to afford a white solid (0.22g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.59 (s, 1H), 9.77 (s, 1H), 8.35 – 8.19 (m, 2H), 7.74 – 7.64 (m, 1H), 7.59 – 7.51 (m, 2H), 7.41 (d, *J* = 8.7 Hz, 1H), 6.71 (d, *J* = 8.7 Hz, 1H), 6.04 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.92, 164.15, 155.59, 155.41, 134.48, 132.45, 130.80 (2C), 128.96 (2C), 128.17, 126.23, 116.04, 109.15; IR (film) 3290, 1730, 1627, 1502, 1448, 1317, 1240, 1089, 1055, 796, 704 cm^{-1}; HRMS (MALDI) *m/z* calcd. for $C_{14}H_{10}O_5$ $[M+H]^+$: 259.0601, found: 259.0601.



A mixture of alcohol (800.0 mg, 2.75 mmol), phenol (852.1mg, 3.30 mmol) and triphenylphosphine (865.6 mg, 3.30 mmol) in THF (15 mL) was cooled to 0 °C and diisopropyl azodicarboxylate (0.64 mL, 3.30 mmol) was added dropwise. After the addition was completed, the reaction was stirred at 0 °C for 2 h, then warmed to r.t. and stirred for 16 h. The reaction was concentrated and purified by flash column chromatography (30% ethyl acetate/hexanes) to provide a light yellow oil (1.15 g, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.32 (s, 1H), 9.80 (s, 1H), 8.29 – 8.22 (m, 2H), 7.68 – 7.62 (m, 1H), 7.53 (dd, *J* = 8.4, 7.2 Hz, 2H), 7.47 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.52 (ddd, *J* = 8.3, 6.7, 1.3 Hz, 1H), 5.32 (tq, *J* = 6.9, 1.5 Hz, 1H), 4.56 (s, 2H), 2.88 (d, *J* = 6.9 Hz, 2H), 2.40 (q, *J* = 7.2 Hz, 2H), 2.35 (q, *J* = 1.3 Hz, 3H), 2.29 – 2.24 (m, 2H); ^{13}C NMR (126 MHz, Chloroform-d) δ 194.92, 164.06, 157.31, 155.26, 134.81, 133.83, 132.65, 131.60, 130.53 (2C), 128.90, 128.72 (2C), 127.44, 125.93, 119.07, 116.52, 104.99, 103.14, 72.29, 36.20, 33.46, 23.97, 17.18; IR (film) 3458,3269, 3062, 2951, 2848, 2752, 2247, 1741, 1645, 1446, 1269, 1176, 1095, 1076, 1056, 1002, 912, 852, 786, 731, 705, 646, 542 cm^{-1}; HRMS (MALDI) *m/z* calcd. for $C_{24}H_{22}INO_5Li$ $[M+Li]^+$: 538.0697, found: 538.0685.

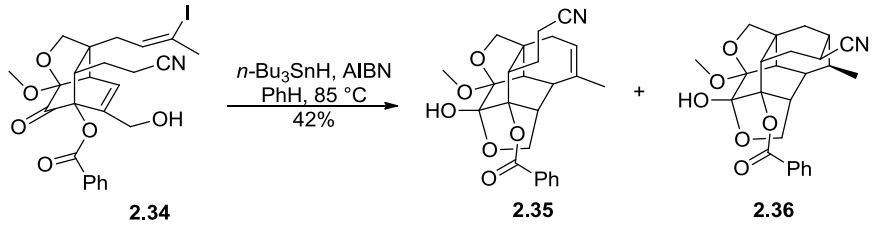


A solution of phenol (10.0 mg, 0.0188 mmol) in methanol (0.90 mL) was heated to 67 °C, to which a solution of iodobenzene diacetate (13.3 mg, 0.0414 mmol) in methanol (0.70 mL) was added over 40 min via syringe pump. After the addition was completed, the reaction was stirred for additional 2 h then cooled to r.t. and concentrated. The crude product was purified by column chromatography (50-75% diethyl ether/hexanes) to afford a white solid (6.4 mg, 61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 8.11 (d, J = 7.7 Hz, 2H), 7.67 – 7.57 (m, 1H), 7.56 – 7.40 (m, 2H), 7.13 (d, J = 7.0 Hz, 1H), 5.45 (td, J = 6.7, 1.6 Hz, 1H), 4.18 (d, J = 8.7 Hz, 1H), 4.11 – 3.95 (m, 1H), 3.63 (s, 3H), 3.31 (d, J = 7.0 Hz, 1H), 2.66 – 2.55 (m, 1H), 2.60 (q, J = 1.3 Hz, 3H), 2.29 (qd, J = 16.4, 15.8, 6.7 Hz, 2H), 1.96 – 1.80 (m, 1H), 1.80 – 1.63 (m, 1H), 1.39 – 0.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.75, 187.06, 164.92, 139.48, 133.88, 130.16 (2C), 129.31, 128.82 (2C), 128.74 (2C), 119.29, 107.60, 98.49, 86.64, 78.57, 53.51, 50.72, 49.74, 48.39, 40.20, 34.09, 23.79, 17.46; IR (film) 2954, 2924, 2853, 2245, 1767, 1727, 1692, 1451, 1274, 1175, 1088, 1067, 1049, 710 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{25}INO_6$ $[M+H]^+$: 562.0721, found: 562.0721.



2.22 **2.23**

Sodium borohydride (1.94 mg, 0.0513 mmol) in methanol (1.0 mL) was added to a solution of α,β-unsaturated aldehyde (57.6 mg, 0.103 mmol) in dichloromethane (0.50 mL) and methanol (1.0 mL) at 0 °C. After stirring at 0 °C for 30 min, the reaction was warmed to r.t. and stirred for 10 min., then quenched with 0.1 M HCl (2.5 mL), extracted with ethyl acetate for three times. The extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (50 % ethyl acetate/hexanes) to afford a white solid (36.2 mg, 62% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 – 7.98 (m, 2H), 7.68 – 7.56 (m, 1H), 7.54 – 7.41 (m, 2H), 6.26 (dt, *J* = 6.9, 1.6 Hz, 1H), 5.46 (td, *J* = 6.7, 1.6 Hz, 1H), 4.45 (dd, *J* = 5.8, 1.6 Hz, 2H), 4.22 – 4.02 (m, 2H), 3.61 (s, 3H), 3.48 (t, *J* = 6.2 Hz, 1H), 3.07 (d, *J* = 6.9 Hz, 1H), 2.58 (q, *J* = 1.3 Hz, 3H), 2.49 (ddd, *J* = 16.8, 9.1, 6.2 Hz, 1H), 2.40 – 2.21 (m, 3H), 1.99 – 1.77 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.83, 164.56, 140.67, 134.05, 130.05 (2C), 129.44, 129.21, 128.94 (2C), 123.50, 119.21, 106.91, 99.69, 89.34, 79.67, 60.85, 53.05, 50.42, 48.23, 46.21, 39.76, 34.10, 23.57, 17.46; IR (film) 3493, 2955, 2924, 2853, 2247, 1758, 1727, 1450, 1267, 1175, 1089, 1061, 711 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}INO_6$ $[M+H]^+$: 564.0877, found: 564.0878.



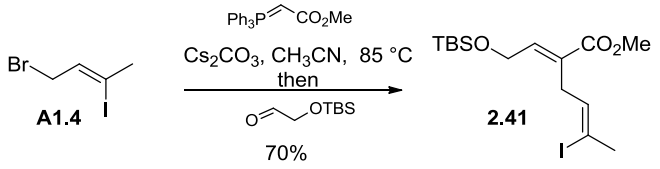
2.34 **2.35** **2.36**

A solution of vinyl iodide (10.0 mg, 0.0178 mmol) in benzene (0.50 mL) was heated to 85 °C, to which tributyltin hydride (0.10 M in benzene, 0.43 mL) and azobisisobutyronitrile (0.01 M in benzene, 0.36 mL) were added simultaneously via syringe pumps over 1 h. After the addition was completed, the reaction was stirred for 30 min. then cooled to r.t. and concentrated. The crude product was purified by column chromatography (50-60% ethyl acetate/hexanes) to give product **2.35** (higher R_f, colorless oil, 0.4 mg, 5% yield) and **2.36** (lower R_f, 2.9 mg, colorless oil, 37% yield).

Compound **2.35**: ^{1}H NMR (600 MHz, C_6D_6) δ 8.14 – 8.07 (m, 2H), 7.15 – 7.04 (m, 3H), 4.93 (d, J = 4.9 Hz, 1H), 4.34 (dd, J = 7.6, 3.7 Hz, 1H), 3.95 (s, 1H), 3.67 (s, 3H), 3.52 (d, J = 7.4 Hz, 1H), 3.47 (d, J = 7.7 Hz, 1H), 3.36 (d, J = 7.4 Hz, 1H), 3.21 (d, J = 8.3 Hz, 1H), 2.03 (d, J = 4.1 Hz, 1H), 1.91 (d, J = 3.7 Hz, 1H), 1.89 – 1.75 (m, 2H), 1.74 – 1.68 (m, 2H), 1.61 – 1.52 (m, 1H), 1.52 – 1.46 (m, 1H), 1.45 – 1.37 (m, 1H), 1.36 (s, 3H); ^{13}C NMR (C_6D_6, extracted from HSQC and HMBC) δ 166.35, 136.74, 132.96, 130.02, 129.94 (2C), 128.41 (2C), 120.13, 119.24, 107.49, 106.55, 91.00, 80.70, 73.53, 53.18, 46.51, 42.55, 42.06, 41.12, 40.96, 29.31, 22.98, 21.2, 17.81; IR (film) 3498, 2948, 2927, 2892, 2247, 1713, 1450, 1292, 1257, 1195, 1112,

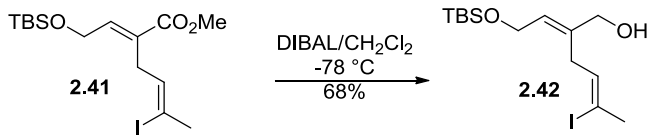
1070, 994, 958, 710 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}NNaO_6$ $[M+Na]^+$: 460.1730, found: 460.1731.

Compound **2.36**: ^1H NMR (600 MHz, C_6D_6) δ 8.26 – 8.21 (m, 2H), 7.15 – 7.04 (m, 3H), 4.07 (dd, *J* = 8.1, 4.4 Hz, 1H), 4.01 (s, 1H), 3.68 (s, 3H), 3.21 – 3.17 (m, 2H), 3.02 (d, *J* = 7.3 Hz, 1H), 2.91 (dd, *J* = 11.9, 7.3 Hz, 1H), 2.75 (d, *J* = 4.4 Hz, 1H), 2.51 (d, *J* = 6.1 Hz, 1H), 1.90 (ddd, *J* = 14.8, 7.2, 1.6 Hz, 1H), 1.73 (q, *J* = 3.7 Hz, 1H), 1.52 (t, *J* = 4.2 Hz, 1H), 1.46 (ddd, *J* = 14.8, 11.9, 6.4 Hz, 1H), 1.29 (dd, *J* = 13.2, 3.1 Hz, 1H), 1.25 (d, *J* = 4.1 Hz, 1H), 1.02 – 0.95 (m, 1H), 0.53 (d, *J* = 7.1 Hz, 3H), 0.43 – 0.36 (m, 1H); ^{13}C NMR (C_6D_6, extracted from HSQC and HMBC) δ 166.34, 133.15, 131.39, 130.09 (2C), 128.38 (2C), 123.44, 107.68, 107.66, 88.36, 78.00, 73.50, 53.11, 49.39, 40.85, 39.60, 37.58, 36.87, 36.30, 35.87, 27.49, 22.89, 21.46, 15.19; IR (film) 3499, 2948, 2927, 2875, 2235, 1713, 1454, 1269, 1195, 1112, 1100, 982, 710 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{28}NO_6$ $[M+H]^+$: 438.1911, found: 438.1911.



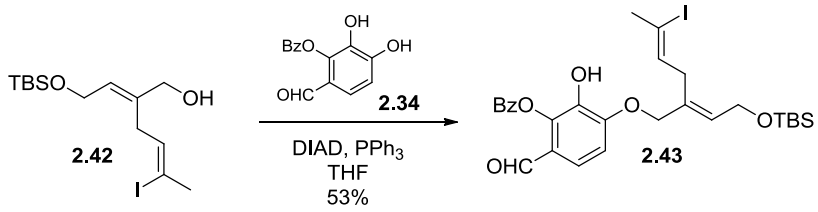
A mixture of methyl (triphenylphosphoranylidene)acetate (5.22 g, 15.6 mmol), vinyl bromide (4.15 g, 15.9 mmol) and cesium carbonate (5.08 g, 15.6 mmol) in acetonitrile (80 mL) was heated at 85 °C for 4 h, and then the hot reaction mixture was filtered through a Celite pad. The filtrate was concentrated on rotovap and placed under vacuum for 15 min to remove any residual bromide. The resultant phosphorane intermediate was re-dissolved in acetonitrile (80 mL) and (*tert*-butyldimethylsilyloxy)

acetaldehyde (2.72 g, 15.6 mmol) was added. The solution was stirred at 85 °C for 15 h and cooled to r.t. Acetonitrile was removed on rotovap, and hexanes were added to the residue while a solid crushed out, which was filtered off and washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography (25% diethyl ether/hexanes) to afford a light yellow oil (4.50 g, 70% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.85 (t, J = 5.6 Hz, 1H), 5.39 (tq, J = 6.5, 1.5 Hz, 1H), 4.43 (d, J = 5.6 Hz, 2H), 3.76 (s, 2H), 3.07 (d, J = 6.5 Hz, 2H), 2.48 (q, J = 1.5 Hz, 2H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.61, 144.14, 132.48, 128.55, 101.41, 61.10, 52.11, 35.49, 33.64, 26.05 (3C), 18.45, -5.06 (2C); IR (film) 2953, 2927, 2856, 2362, 1716, 1463, 1436, 1251, 1205, 1107, 1085, 1041, 837, 777 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{15}H_{28}IO_3Si$ $[M+H]^+$: 411.0847, found: 411.0850.



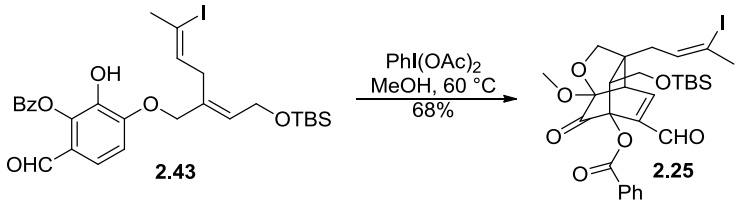
To a solution of ester (7.82 g, 19.1 mmol) in dichloromethane (45 mL) at -78 °C, was added DIBAL (1.0 M in dichloromethane, 47.2 mL) dropwise. The reaction was stirred at -78 °C for 3 h then quenched by saturated Rochelle's salt solution (20 mL) and diluted with ethyl acetate (300 mL). The mixture was allowed to warm to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford a colorless oil (4.93 g, 68% yield). ^{1}H NMR (500

MHz, $CDCl_3$) δ 5.64 (ttd, *J* = 5.3, 1.4, 0.6 Hz, 1H), 5.37 (tq, *J* = 6.8, 1.5 Hz, 1H), 4.27 (dt, *J* = 6.2, 1.2 Hz, 2H), 4.06 (s, 2H), 2.90 (dt, *J* = 6.8, 1.2 Hz, 2H), 2.50 (q, *J* = 1.4 Hz, 3H), 1.47 (s, 1H), 0.91 (s, 9H), 0.09 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.47, 132.74, 127.32, 102.12, 66.71, 60.12, 36.48, 33.68, 26.17 (3C), 18.58, -4.92 (2C); IR (film) 3365, 2953, 2927, 2856, 1463, 1255, 1107, 1066, 835 777 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{14}H_{27}IO_2SiLi$ $[M+Li]^+$: 389.0980, found: 389.0976.

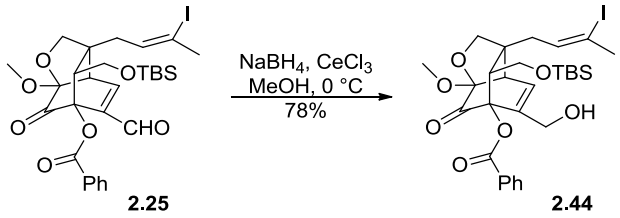


To a solution of triphenylphosphine (850 mg, 3.24 mmol) in THF (8.0 mL) was added diisopropyl azodicarboxylate (0.63 mL, 3.24 mmol) dropwise at 0 °C. After stirring for 30 min., a solution of alcohol (411 mg, 1.08 mmol) and phenol (837 mg, 3.24 mmol) in THF (2.5 mL) was added dropwise. The reaction was allowed to warm to r.t. naturally and stirred for total 24 h t. Removal of solvent and purification by column chromatography (20% ethyl acetate/hexanes) afforded a light yellow oil (353 mg, 53% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 11.33 (s, 1H), 9.76 (s, 1H), 8.31 – 8.18 (m, 2H), 7.70 – 7.57 (m, 1H), 7.54 – 7.46 (m, 2H), 7.43 (d, *J* = 8.8 Hz, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 5.70 (tt, *J* = 6.0, 1.1 Hz, 1H), 5.28 (tq, *J* = 6.8, 1.5 Hz, 1H), 4.54 (d, *J* = 1.3 Hz, 2H), 4.22 (d, *J* = 6.0 Hz, 2H), 2.86 (d, *J* = 6.8 Hz, 2H), 2.30 (q, *J* = 1.5 Hz, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.85, 163.98, 157.58, 155.23, 133.71, 132.55, 132.00, 131.98, 131.22, 130.52 (2C), 128.92, 128.64 (2C), 127.40, 116.40, 104.99, 102.47, 72.80, 59.94, 36.40, 33.40, 26.00 (3C), 18.36, -

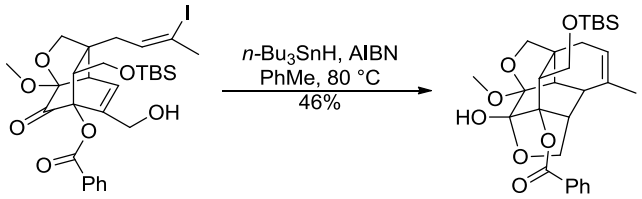
5.08 (2C); IR (film) 2953, 2927, 2854, 1743, 1647, 1506, 1242, 1105, 1058, 835, 705 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{28}H_{36}IO_6Si$ $[M+H]^+$: 623.1320, found: 623.1330.



A solution of phenol (153.0 mg, 0.246 mmol) in methanol (16.0 mL) was heated to 60 °C, to which a solution of iodobenzene diacetate (174.2 mg, 0.541mmol) in methanol (8.0 mL) was added over 2.5 h via syringe pump. After stirring for additional 2 h the reaction was cooled to r.t. and concentrated. The crude product was purified by column chromatography (20% diethyl ether/hexanes) to afford a light yellow solid (108.8 mg, 68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 8.16 (d, *J* = 7.7 Hz, 2H), 7.65 – 7.56 (m, 1H), 7.52 – 7.42 (m, 2H), 7.08 (d, *J* = 7.1 Hz, 1H), 5.53 (td, *J* = 7.0, 1.5 Hz, 1H), 4.15 (d, *J* = 8.2 Hz, 1H), 4.04 – 3.87 (m, 2H), 3.75 (dd, *J* = 11.5, 5.9 Hz, 1H), 3.62 (s, 3H), 3.35 (d, *J* = 7.0 Hz, 2H), 2.71 – 2.42 (m, 2H), 2.59 (d, *J* = 1.5 Hz, 3H), 0.82 (s, 9H), -0.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.15, 185.85, 164.46, 139.68, 138.55, 133.68, 130.24 (2C), 129.69 (2C), 129.54, 128.63 (2C), 106.61, 99.13, 78.81, 59.60, 53.25, 51.68, 48.83 (2C), 37.07, 34.17, 26.17 (3C), 18.45, -5.41, -5.46; IR (film) 2954, 2929, 2856, 1766, 1729, 1695, 1470, 1451, 1274, 1179, 1091, 912, 837, 780, 709 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{29}H_{37}INaO_7Si$ $[M+Na]^+$: 675.1245, found: 675.1250.

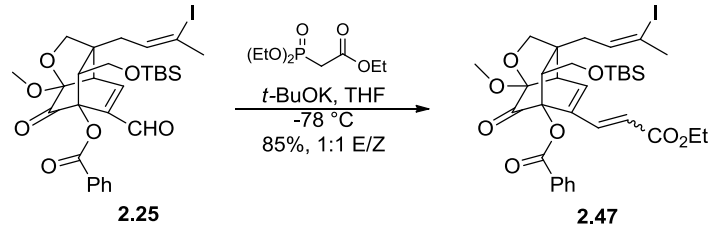


To an ice-water cooled mixture of α,β-unsaturated aldehyde (20.0 mg, 0.0307 mmol) and cerium (III) chloride heptahydrate (57.0 mg, 0.153 mmol) in methanol (0.62 mL) was added sodium borohydride (3.5 mg, 0.0925 mmol) in one portion. The reaction was stirred at 0 °C for 2 h then quenched by saturated NH_4Cl solution (0.2 mL) and extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (25% ethyl acetate/hexanes) to afford a colorless oil (15.7 mg, 78% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 – 7.98 (m, 2H), 7.69 – 7.53 (m, 1H), 7.47 (m, 2H), 6.18 (dt, *J* = 6.8, 1.6 Hz, 1H), 5.51 (td, *J* = 7.5, 7.0, 1.8 Hz, 1H), 4.45 (qd, *J* = 14.8, 4.0 Hz, 2H), 4.09 (d, *J* = 8.1 Hz, 1H), 4.05 (d, *J* = 8.1 Hz, 1H), 3.84 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.74 (dd, *J* = 11.3, 5.2 Hz, 1H), 3.62 (s, 3H), 3.58 (t, *J* = 5.4 Hz, 1H), 3.07 (d, *J* = 6.8 Hz, 1H), 2.59 – 2.51 (m, 1H), 2.56 (s, 3H), 2.42 – 2.33 (m, 1H), 2.05 (t, *J* = 5.8 Hz, 1H), 0.76 (s, 9H), -0.11 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.29, 163.96, 140.98, 133.55, 130.26, 130.01 (2C), 129.96, 128.65 (2C), 122.07, 105.68, 99.82, 87.66, 79.59, 60.96, 60.43, 52.92, 49.82, 47.95 (2C), 38.21, 34.07, 26.06 (3C), 18.45, -5.40, -5.49; IR (film) 3488, 2954, 2927, 2855, 1759, 1729, 1451, 1275, 1251, 1093, 1004, 837, 780, 709 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{29}H_{40}IO_7Si$ $[M+H]^+$: 655.1582, found: 655.1579.



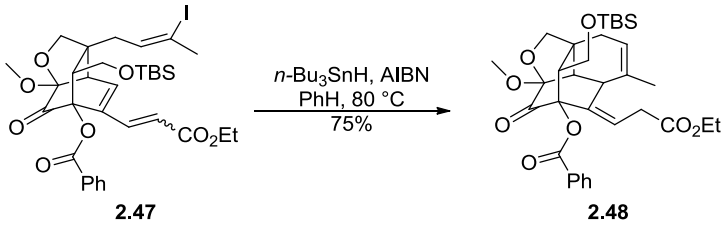
2.44 **2.45**

A solution of vinyl iodide (15.0 mg, 0.0229 mmol) in toluene (1.30 mL) was heated to 80 °C, to which tributyltin hydride (0.10 M in toluene, 0.55 mL) and azobisisobutyronitrile (0.01 M in toluene, 0.46 mL) were added simultaneously via syringe pumps over 1 h. After the addition was completed, the reaction was stirred for additional 2h then cooled to r.t. and concentrated. The crude product was purified by column chromatography (20% ethyl acetate/hexanes) to afford a colorless oil (5.6 mg, 46% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (m, 2H), 7.61 – 7.52 (m, 1H), 7.47 – 7.39 (m, 2H), 5.51 (dt, *J* = 5.1, 1.7 Hz, 1H), 4.41 (dd, *J* = 7.9, 3.7 Hz, 1H), 4.29 (s, 1H), 3.87 (d, *J* = 7.1 Hz, 1H), 3.76 – 3.69 (m, 3H), 3.60 (dd, *J* = 10.6, 3.1 Hz, 1H), 3.58 (s, 3H), 3.18 (dd, *J* = 10.0, 3.1 Hz, 1H), 2.85 – 2.77 (m, 1H), 2.59 (d, *J* = 3.5 Hz, 1H), 2.30 (d, *J* = 4.1 Hz, 1H), 2.02 – 1.92 (m, 1H), 1.96 (d, *J* = 4.2 Hz, 1H), 1.77 (dt, *J* = 2.7, 1.4 Hz, 3H), 0.80 (s, 9H), -0.11 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.12, 135.77, 133.38, 130.74, 129.91 (2C), 128.57 (2C), 121.67, 107.81, 107.06, 89.16, 81.58, 73.84, 61.28, 52.86, 45.18, 44.97, 42.43, 42.34, 41.17, 28.34, 25.93 (3C), 21.99, 18.14, -5.37, -5.53; IR (film) 3529, 2952, 2927, 2855, 1722, 1259, 1093, 1070, 993, 837, 777, 708 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{29}H_{41}O_7Si$ $[M+H]^+$: 529.2616, found: 529.2615.



2.25 **2.47**

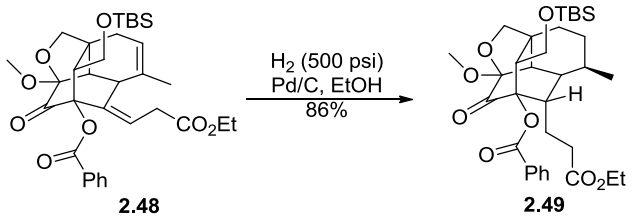
To a solution of triethyl phosphonoacetate (0.041 mL, 0.284 mmol) in THF (0.80 mL) was added potassium *tert*-butoxide (31.9 mg) in portions at 0 °C. After stirring for 15 min., the mixture was cooled to -78 °C and aldehyde (58.0 mg, 0.0945 mmol) in THF (0.20 mL) was added dropwise. The reaction was stirred at -78 °C for 4 h then quenched by saturated NH_4Cl solution (1 mL) and extracted with ethyl acetate (3 × 2 mL). The combined extracts were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (20% ethyl acetate/hexanes) to afford a light yellow oil (56.7 mg, 1:1 E/Z mixture, 85% yield).



2.47 **2.48**

A solution of vinyl iodide (53.0 mg, 0.0733 mmol) in benzene (4.0 mL) was heated to 80 °C, to which tributyltin hydride (0.10 M in benzene, 1.80 mL) and azobisisobutyronitrile (0.01 M in benzene, 1.50 mL) were added simultaneously via syringe pumps over 2 h. After the addition was completed, the reaction was stirred for additional 2 h then cooled to r.t. and concentrated. The crude product was purified by

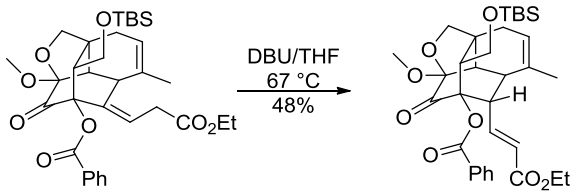
column chromatography (20% ethyl acetate/hexanes) to afford a colorless oil (32.8 mg, 75% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 – 8.01 (m, 2H), 7.65 – 7.52 (m, 1H), 7.46 (m, 2H), 6.33 (td, *J* = 7.5, 1.7 Hz, 1H), 5.65 – 5.54 (m, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 4.08 (d, *J* = 7.4 Hz, 1H), 3.94 (d, *J* = 7.4 Hz, 1H), 3.68 (s, 3H), 3.67 – 3.57 (m, 2H), 3.49 (dd, *J* = 8.6, 3.9 Hz, 1H), 3.33 – 3.28 (m, 3H), 2.86 (ddd, *J* = 18.0, 5.2, 1.8 Hz, 1H), 2.40 (d, *J* = 3.9 Hz, 1H), 2.11 (d, *J* = 18.6 Hz, 1H), 1.87 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 0.75 (s, 9H), -0.17 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.47, 170.72, 163.68, 134.83, 133.28, 132.57, 130.42, 130.01 (2C), 128.54 (2C), 124.04, 121.40, 104.14, 85.49, 82.21, 61.31, 61.16, 53.16, 47.22, 45.40, 43.19, 36.48, 35.45, 29.71, 25.91 (3C), 24.34, 18.13, 14.30, -5.40, -5.48; IR (film) 2953, 2930, 2856, 1759, 1729, 1268, 1252, 1176, 1091, 1001, 837, 777, 707 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{33}H_{45}O_8Si$ $[M+H]^+$: 597.2878, found: 597.2879.



2.48 **2.49**

In a 4-mL vial, diene (3.0 mg, 0.00503 mmol) was dissolved in ethanol (0.20 mL) and palladium on carbon (10 wt%, 3.0 mg) was added. The vial was placed in a hydrogenation bomb and stirred at r.t. under 500 psi of H_2 for 16 h. The reaction mixture was then filtered through a Celite pad and washed with ethyl acetate. The filtrate was concentrated and purified by column chromatrography (20% ethyl acetate/hexanes) to afford a colorless oil (2.6 mg, 86% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.07 – 8.00 (m, 2H), 7.58 – 7.52 (m, 1H), 7.47 – 7.39 (m, 2H), 4.16 (q, *J* =

7.1 Hz, 2H), 4.02 (dd, *J* = 10.9, 7.8 Hz, 1H), 3.84 (d, *J* = 6.8 Hz, 1H), 3.80 (dd, *J* = 10.9, 5.3 Hz, 1H), 3.71 (dd, *J* = 6.8, 0.8 Hz, 1H), 3.70 (s, 3H), 3.57 (dd, *J* = 7.7, 5.4 Hz, 1H), 2.57 (ddd, *J* = 15.7, 8.6, 6.9 Hz, 1H), 2.45 (ddd, *J* = 15.7, 8.6, 6.3 Hz, 1H), 2.32 (m, 1H), 2.11 (q, *J* = 6.6 Hz, 1H), 2.01 (ddt, *J* = 15.1, 8.7, 6.4 Hz, 1H), 1.89 (d, *J* = 2.7 Hz, 1H), 1.86 – 1.82 (m, 1H), 1.75 – 1.61 (m, 2H), 1.46 – 1.25 (m, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.75 (s, 9H), -0.14 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (126 MHz, Chloroform-d) δ 200.10, 173.40, 164.15, 133.08, 130.48, 130.00 (2C), 128.45 (2C), 103.95, 85.71, 82.20, 60.52, 58.94, 53.22, 53.16, 44.51, 44.25, 38.92, 36.02, 35.26, 32.91, 28.81, 27.96, 27.71, 25.92 (3C), 19.55, 18.23, 14.44, -5.54 (2C); IR (film) 2953, 2929, 2856, 1759, 1729, 1266, 1256, 1090, 837, 778, 707 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{33}H_{49}O_8Si$ $[M+H]^+$: 601.3191, found: 601.3192.

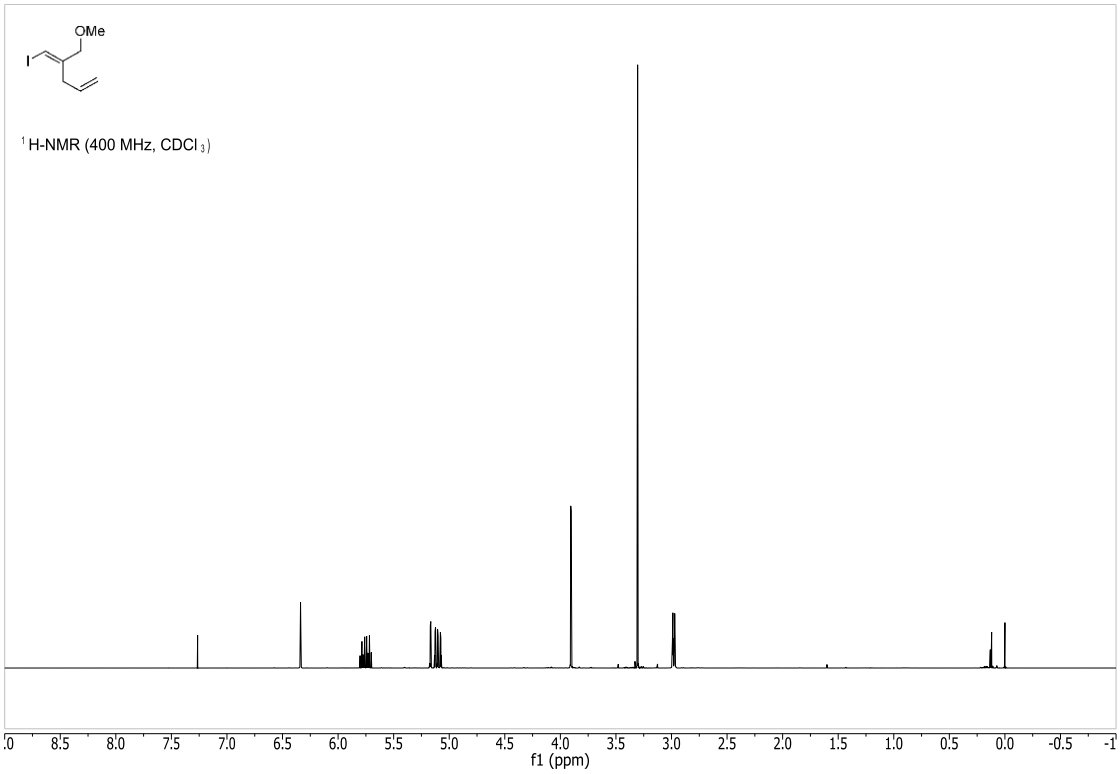


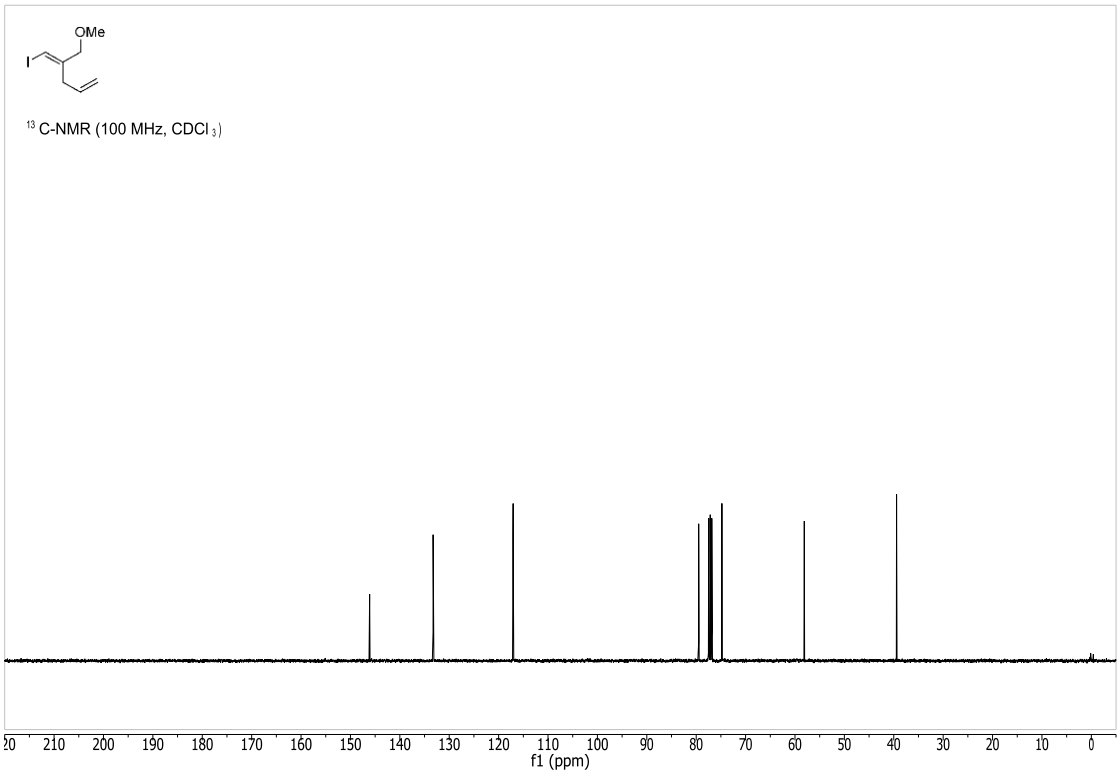
2.47 **2.50**

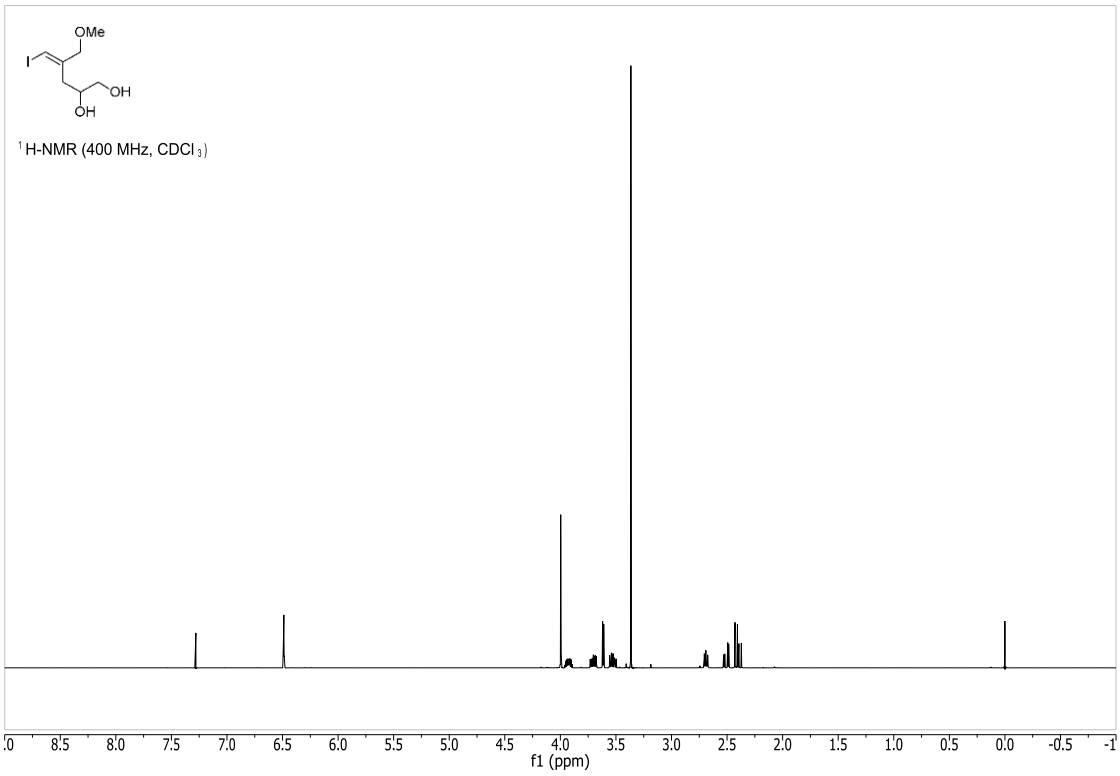
A mixture of diene (27.7 mg, 0.0464 mmol) and 1, 8-diazabicyclo [5.4.0] undec-7-ene (0.02 mL, 0.139 mmol) in THF (0.20 M, 0.05 mL) was heated to 67 °C and stirred for 3 h. The reaction mixture was then cooled to r.t. and concentrated. Purification by column chromatography (10-20% ethyl acetate/hexanes) provided a colorless oil (13.2 mg, 48%) and recovered starting material (8.2 mg, 30%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.90 (m, 2H), 7.60 – 7.51 (m, 1H), 7.46 – 7.34 (m, 2H), 6.72 (dd, *J* = 15.5, 9.3 Hz, 1H), 5.99 (dd, *J* = 15.5, 1.0 Hz, 1H), 5.54 (d, *J* = 4.4 Hz,

1H), 4.30 – 4.11 (m, 2H), 4.02 (d, J = 7.1 Hz, 1H), 3.89 (d, J = 7.1 Hz, 1H), 3.81 (dd, J = 10.6, 9.7 Hz, 1H), 3.75 – 3.70 (m, 1H), 3.69 (s, 3H), 3.54 – 3.48 (m, 1H), 2.88 (ddd, J = 18.2, 4.9, 1.7 Hz, 1H), 2.67 (dd, J = 9.2, 2.9 Hz, 1H), 2.38 (m, 1H), 2.30 (d, J = 3.7 Hz, 1H), 2.16 – 2.08 (m, 1H), 1.78 (dt, J = 2.8, 1.5 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 0.80 (s, 9H), -0.12 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.32, 165.76, 163.92, 145.82, 136.87, 133.34, 130.04, 129.93 (2C), 128.52 (2C), 124.49, 121.07, 103.59, 83.83, 82.43, 60.77, 60.28, 53.06, 47.47, 47.34, 45.55, 43.12, 36.46, 28.84, 25.91 (3C), 22.10, 18.12, 14.39, -5.33, -5.47; IR (film) 2952, 2928, 2894, 2855, 1757, 1727, 1263, 1095, 836, 707 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{33}H_{45}O_8Si$ $[M+H]^+$: 597.2878, found: 597.2877.

A1.2 ^{1}H and ^{13}C NMR spectra for Chapter 2






OMe
I
OH
OH
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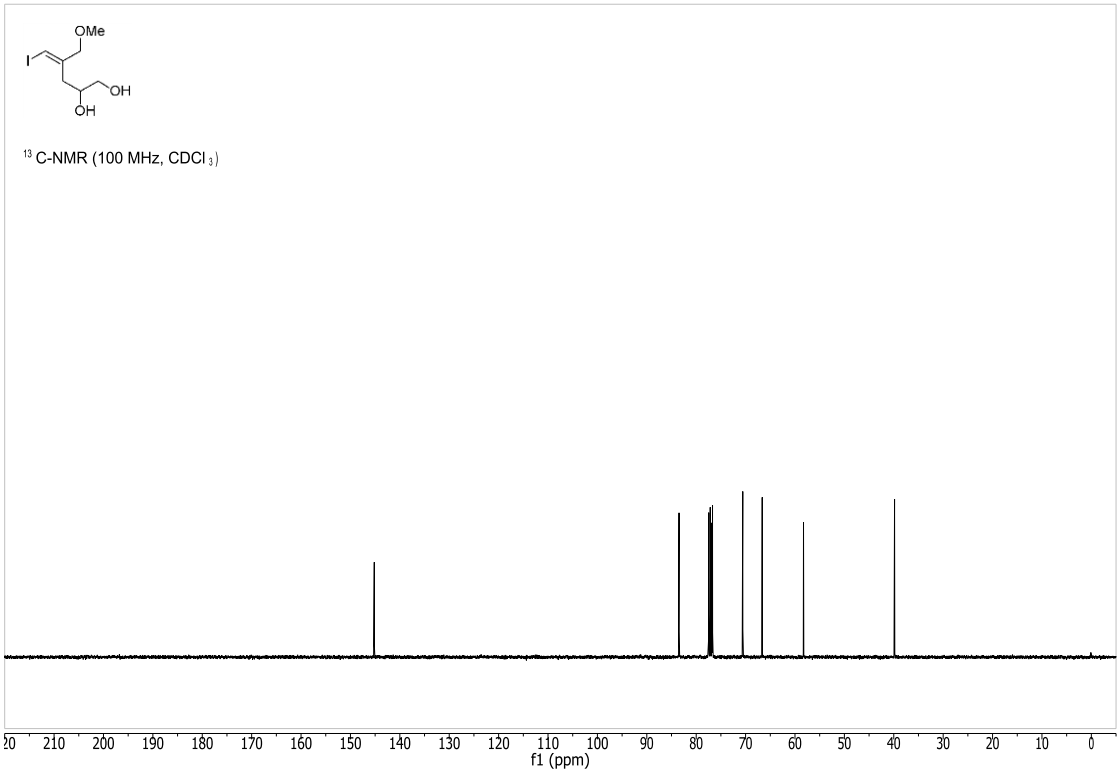
f1 (ppm)


OMe
I
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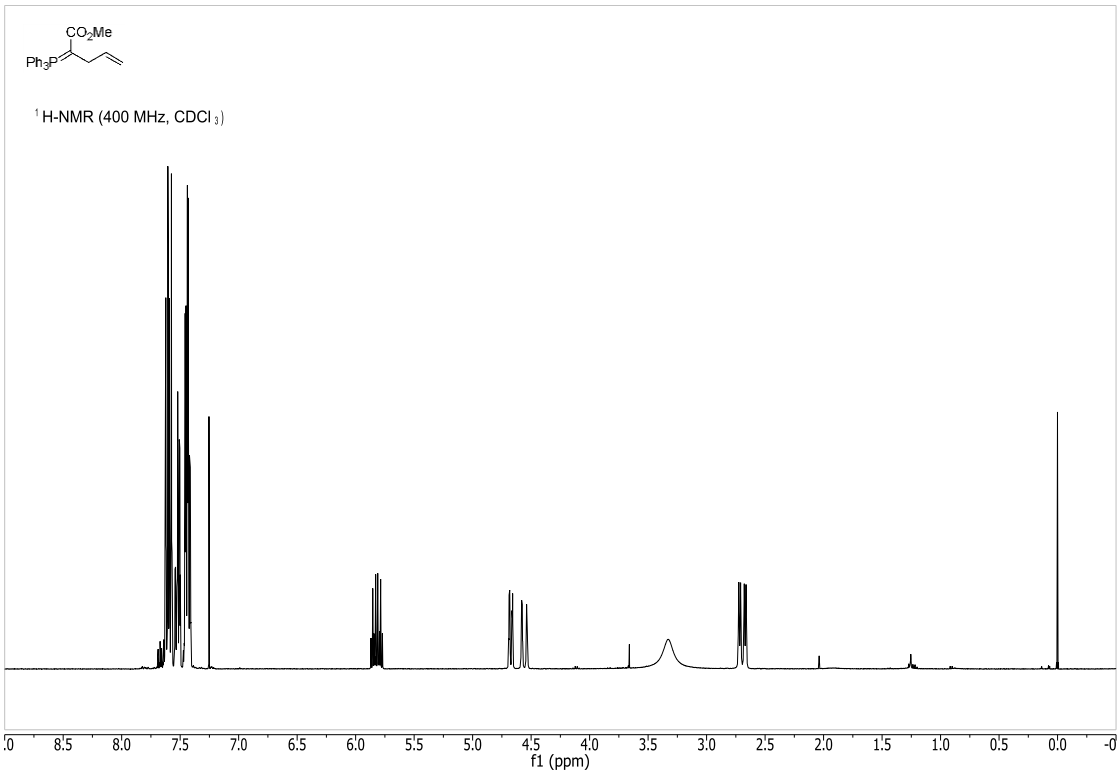
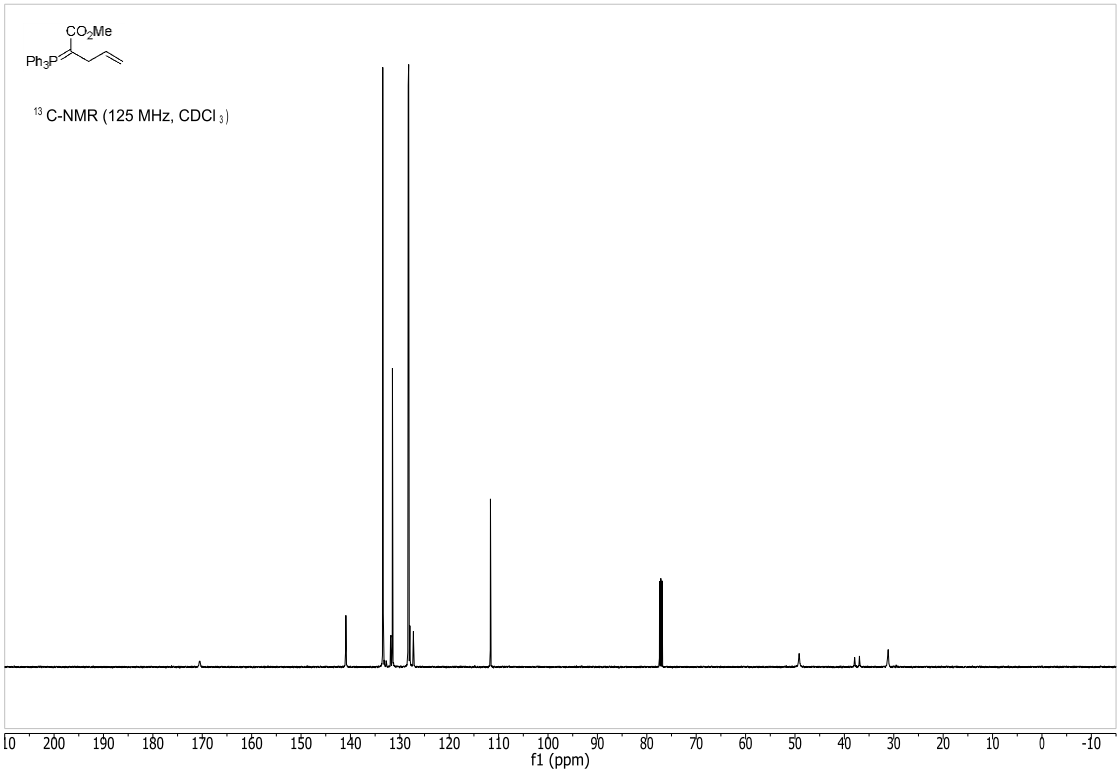
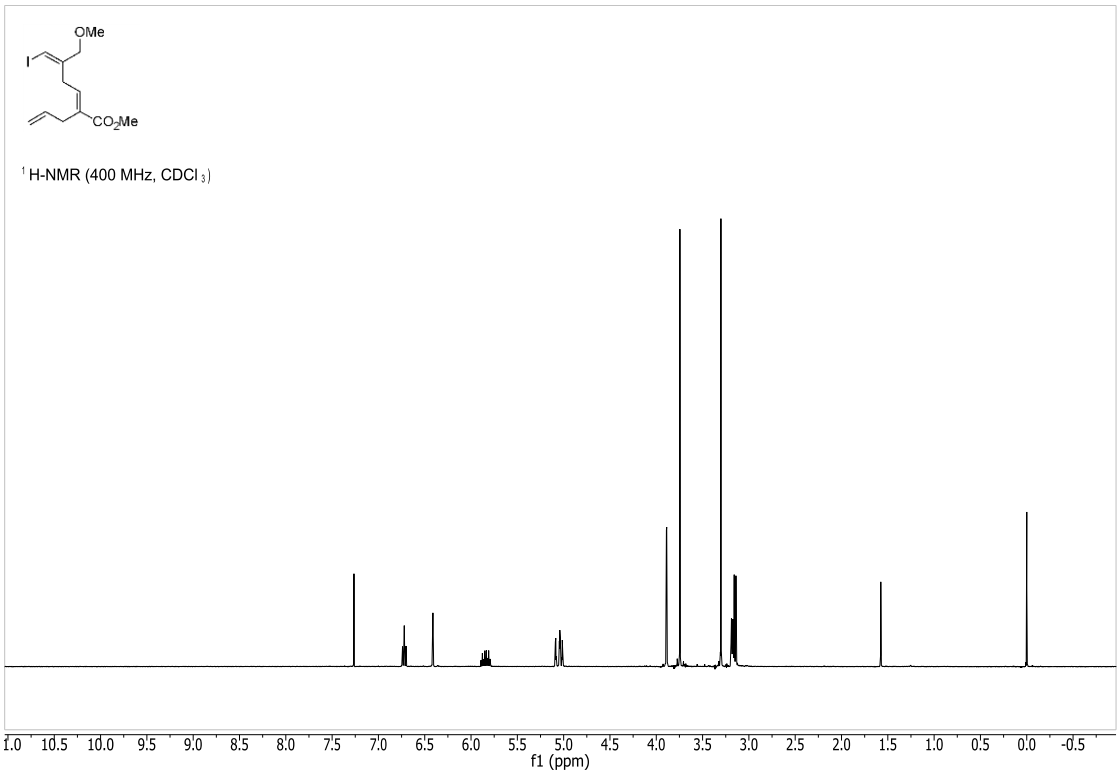
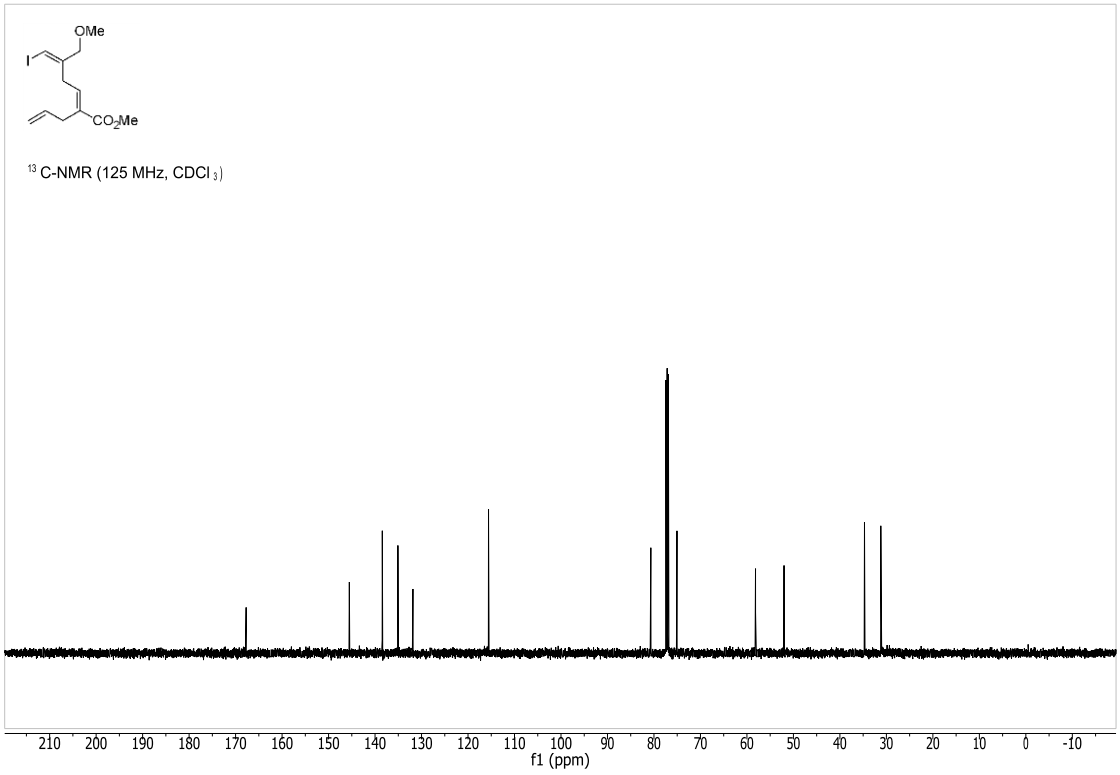
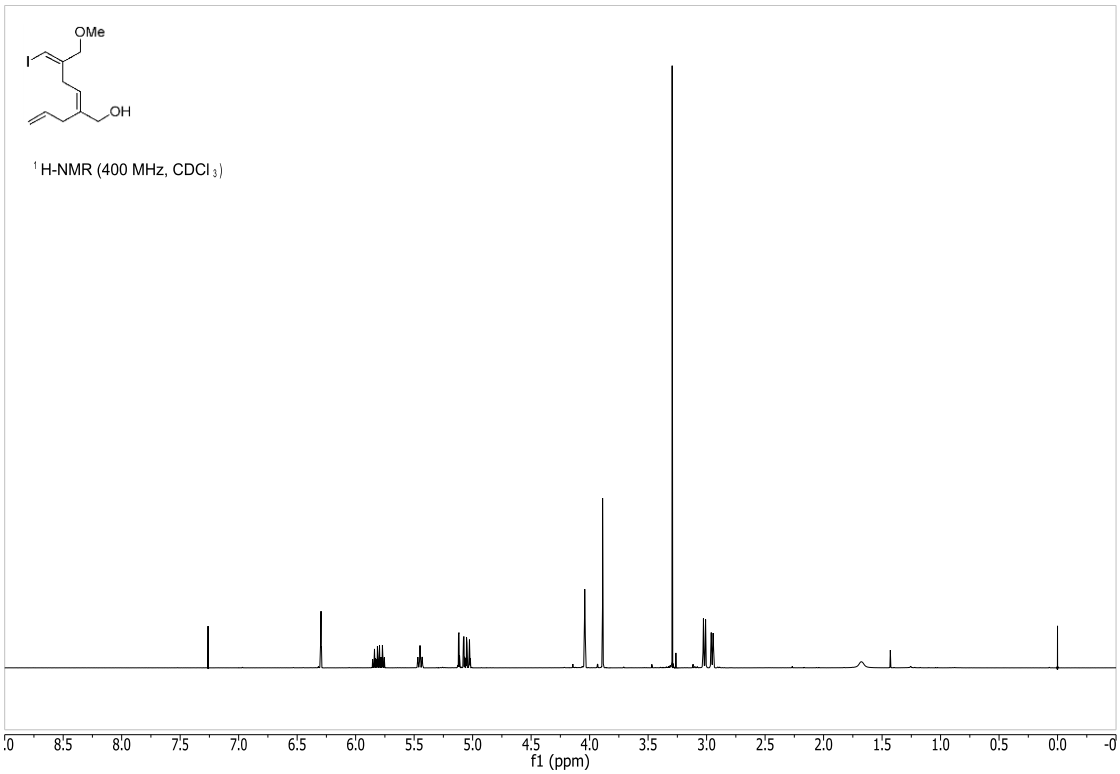
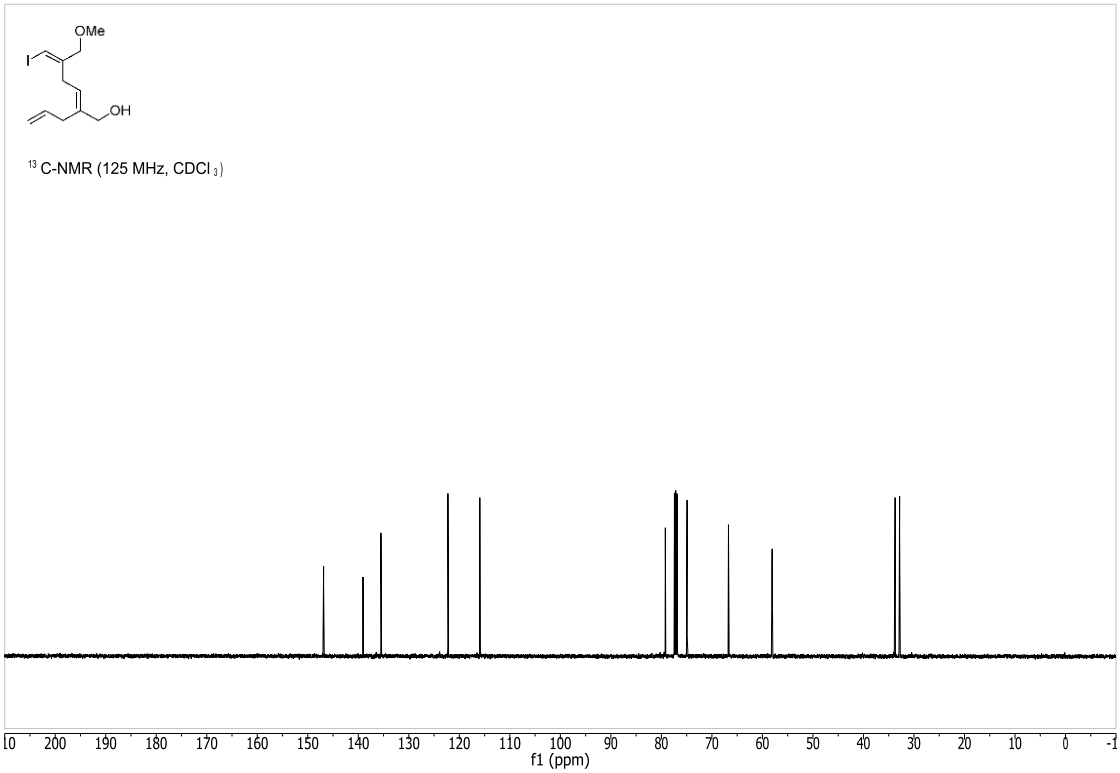

CO2Me
Ph3P
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

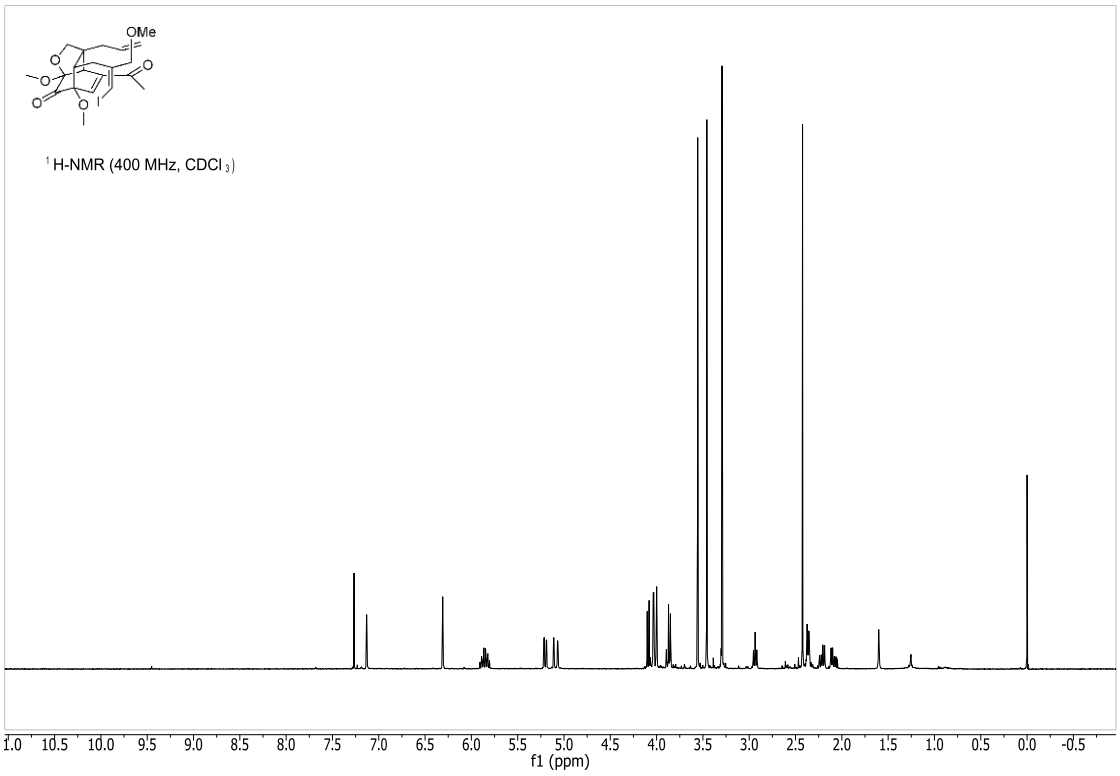

CO2Me
Ph3P
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

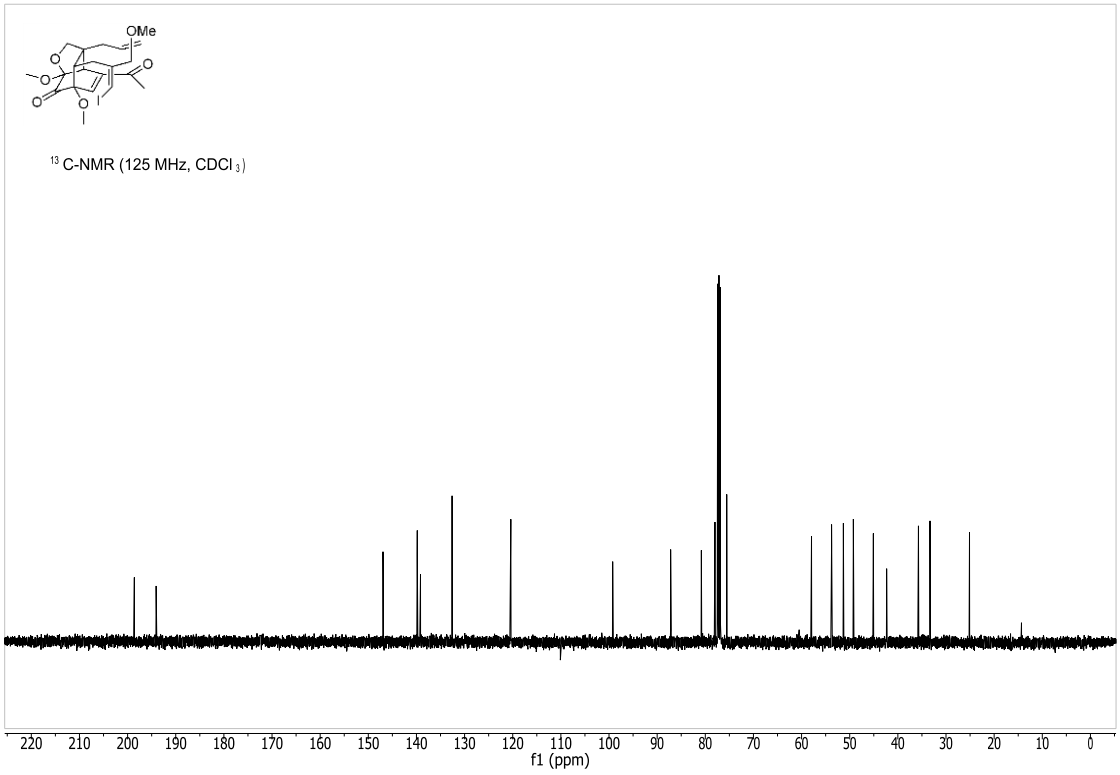

OMe
I
CO2Me
1 H-NMR (400 MHz, CDCl 3)
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

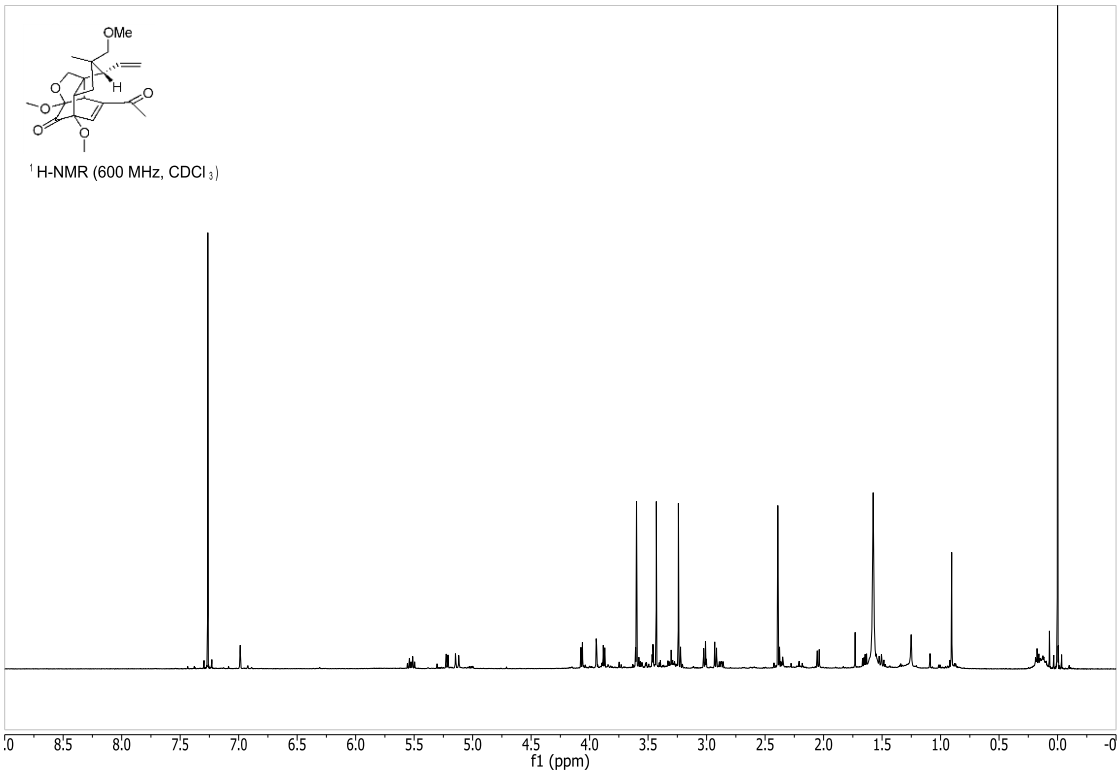

OMe
I
CO2Me
13 C-NMR (125 MHz, CDCl 3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

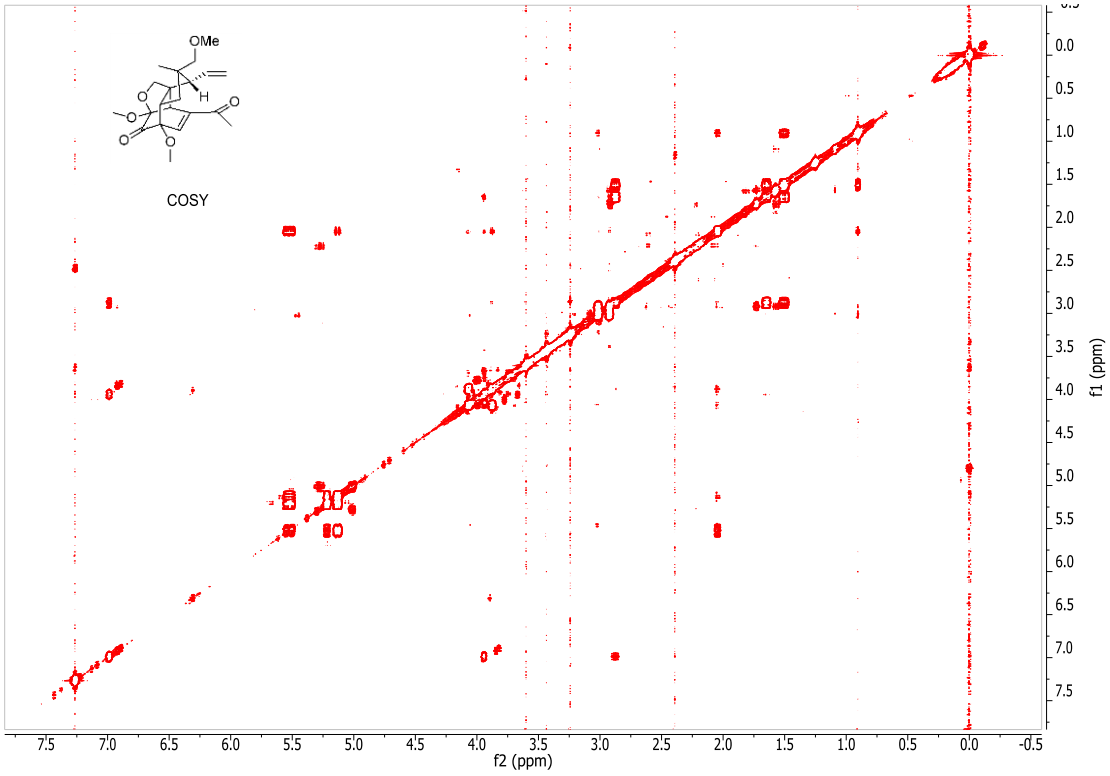

OMe
I
OH
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

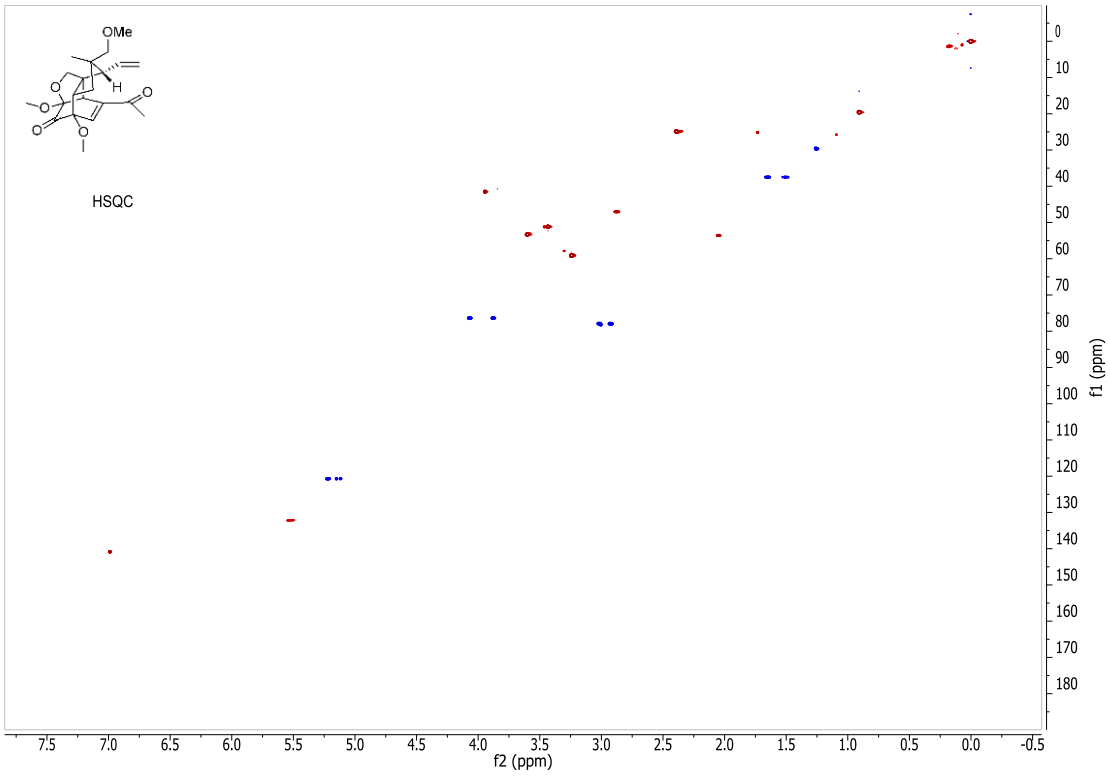

OMe
I
OH
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

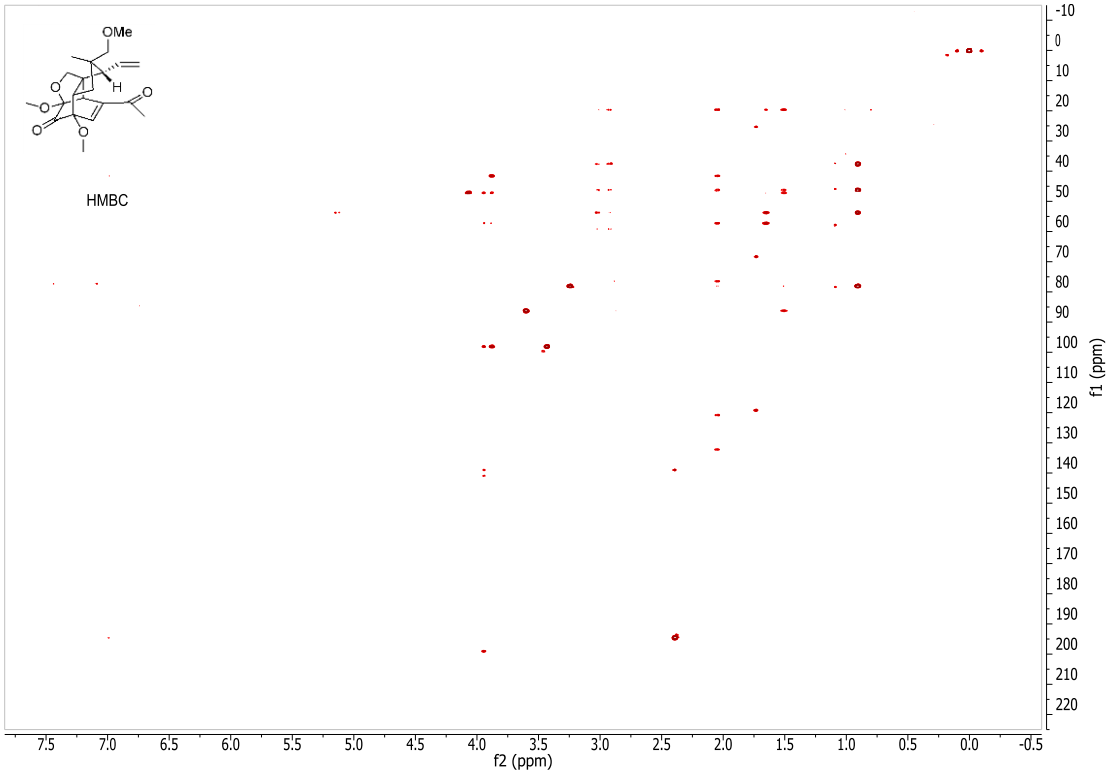

OMe
^{1}H-NMR (400 MHz, CDCl$_3$)
f1 (ppm)


OMe
^{13}C-NMR (125 MHz, CDCl$_3$)
f1 (ppm)


OMe
H
O
O
O
O
O
^{1}H-NMR (600 MHz, CDCl$_3$)
f1 (ppm)


OMe
H
O
O
O
O
O
COSY
f2 (ppm)
f1 (ppm)


OMe
H
O
O
O
O
HSQC
f2 (ppm)
f1 (ppm)


OMe
H
O
O
O
O
HMBC
f2 (ppm)
f1 (ppm)

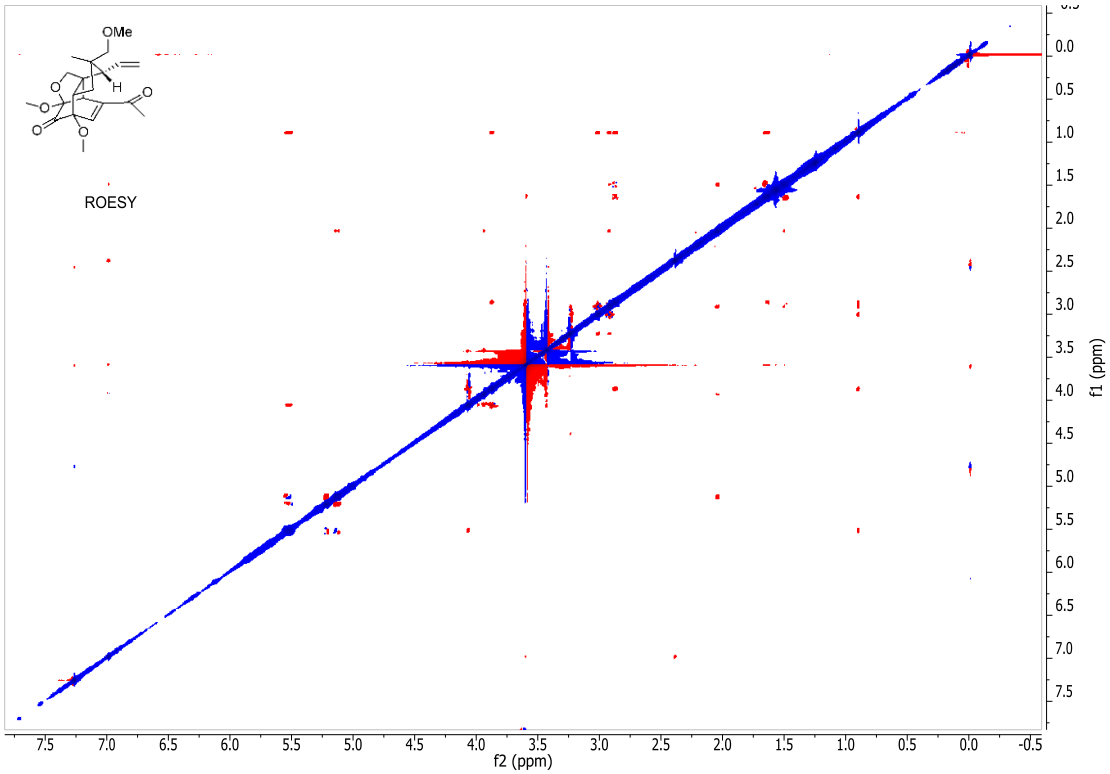
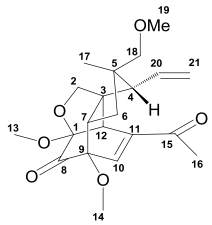
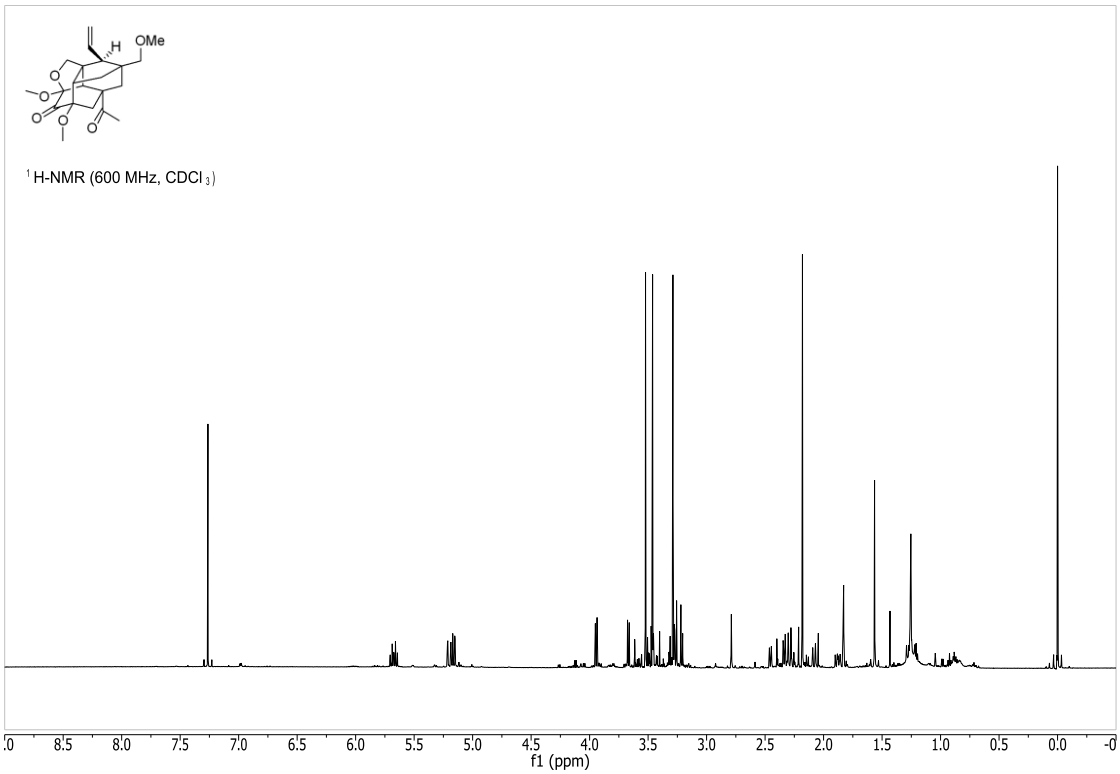
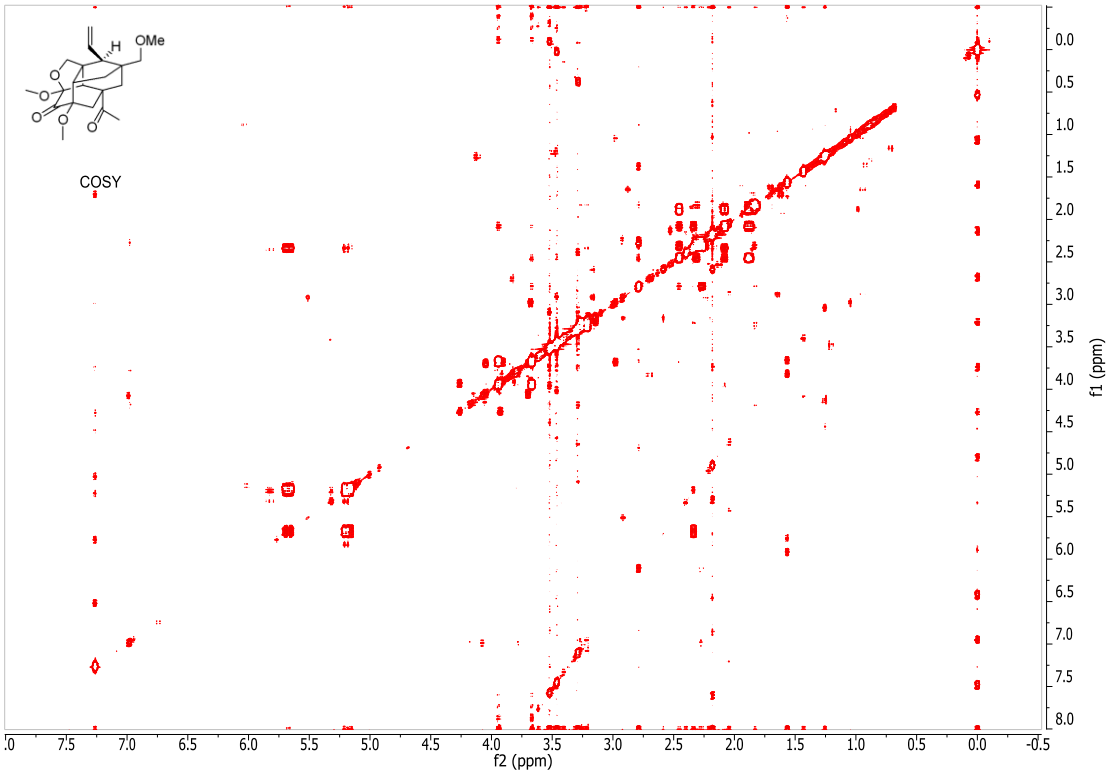

OMe
H
O
O
O
O
ROESY
f2 (ppm)
f1 (ppm)

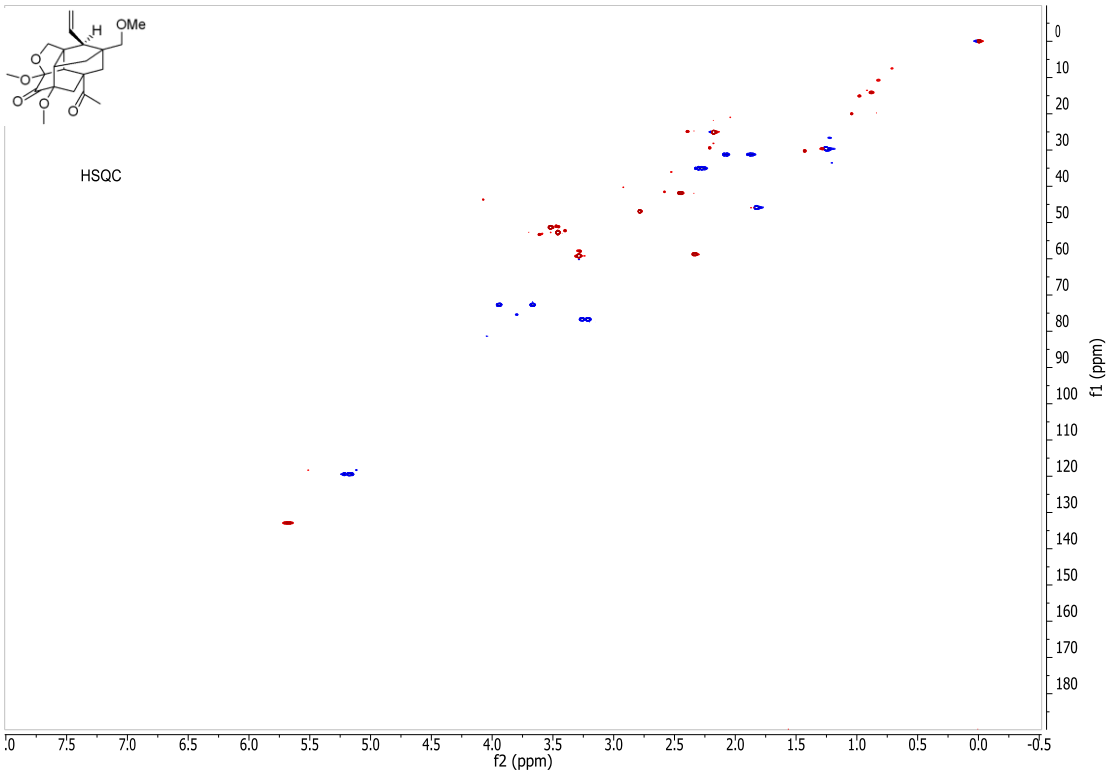
Table A1.1. 2D-NMR Data of Compound **2.19**

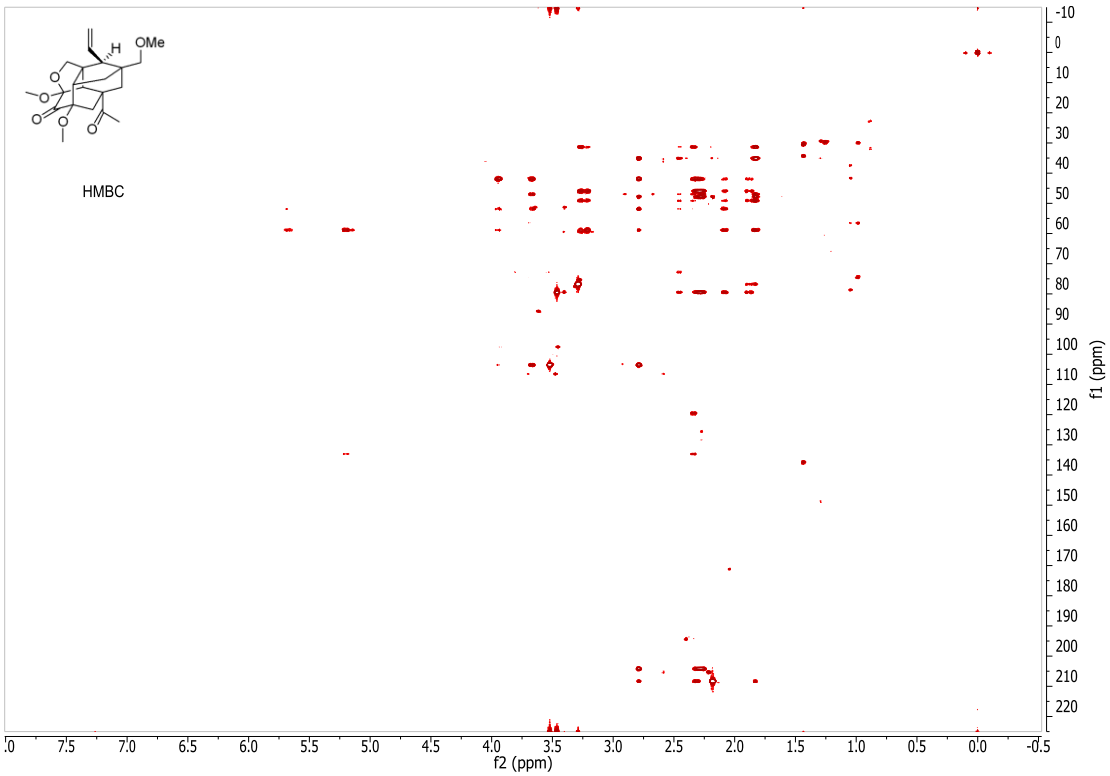


Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	ROESY correlations
1	98.0		Cq			
2a	76.3	4.07	CH_2	H-2b, H-4	C-7	H-12, H-20
2b		3.88	CH_2	H-2a, H-4, H-7	C-1, C-12	H-7
3	57.2		Cq			
4	53.6	2.05	CH	H-2a, H-2b, H-17, H-20, H-21b	C-3, C-5, C-12, C-20, C-21	H-6b, H-12, H-18b, H-21b
5	46.0		Cq			
6a	37.5	1.65	CH_2	H-6b, H-7	C-3, C-4, C-17	H-7, H-14
6b		1.51	CH_2	H-6a, H-7, H-17	C-5, C-7, C-9, C-17	H-4, H-10
7	47.0	2.88	CH	H-2b, H-6a, H-6b, H-10	C-2, C-9, C-10	H-2b, H-6a, H-18a, H-18b
8	198.9		Cq			
9	86.1		Cq			
10	140.9	6.99	CH_3	H-7, H-12	C-15	H-6b, H-14, H-16
11	138.7		Cq			
12	41.5	3.94	CH	H-10	C-1, C-3, C-8, C-10, C-11	H-2a, H-4
13	51.1	3.43	CH_3		C-1	
14	53.3	3.60	CH_3		C-9	H-6a, H-10
15	194.5		Cq			
16	24.8	2.39	CH_3		C-11, C-15	H-10
17	19.5	0.91	CH_3	H-4, H-6b, H-18a	C-4, C-5, C-6, C-18	H-2b, H-6a, H-7, H-18a, H-18b, H-20
18a	77.9	3.02	CH_2	H-17, H-18b	C-5, C-6, C-19	H-7
18b		2.92	CH_2	H-18a	C-5, C-6, C-17, C-19	H-4, H-7
19	59.2	3.24	CH_3		C-18	
20	132.2	5.53	CH	H-4, H-21a, H-21b		H-17, H-2a
21a	120.7	5.22	CH_2	H-20, H-21b		
21b		5.13	CH_2	H-4, H-20, H-21a	C-4	H-4


OMe
H
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)


OMe
H
COSY
f2 (ppm)
f1 (ppm)


OMe
H
HSQC
f1 (ppm)
f2 (ppm)


OMe
H
HMBC
f1 (ppm)
f2 (ppm)

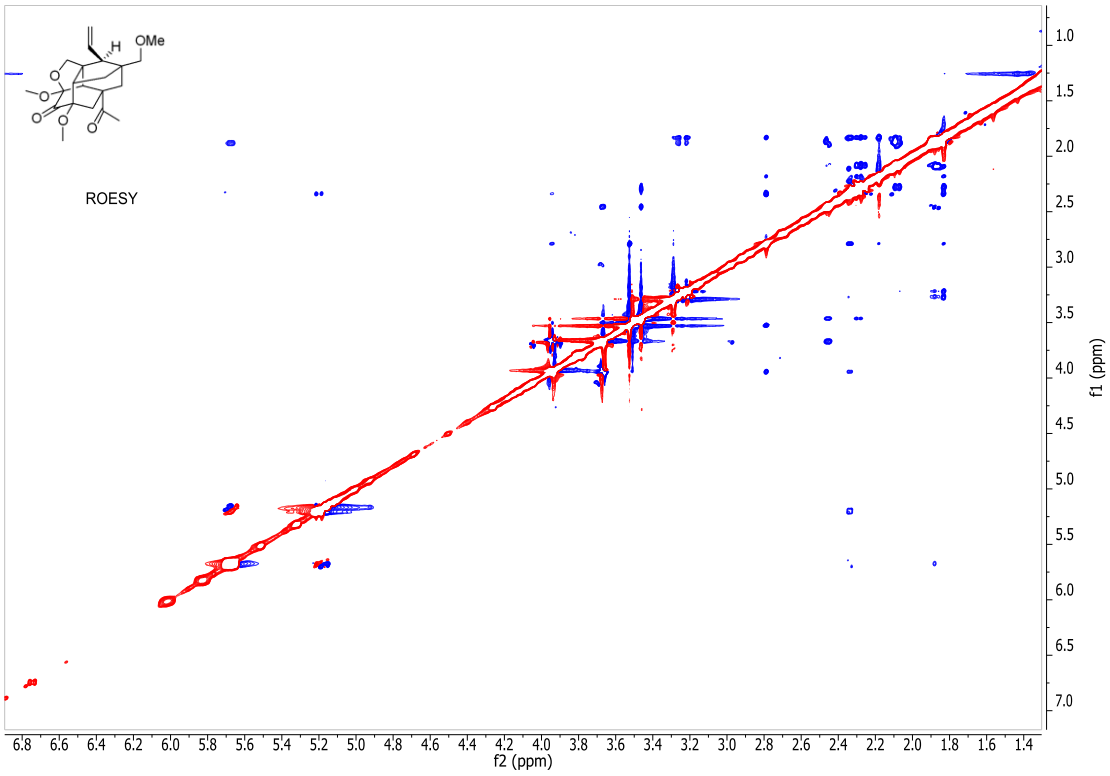
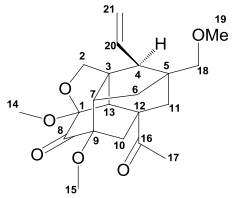
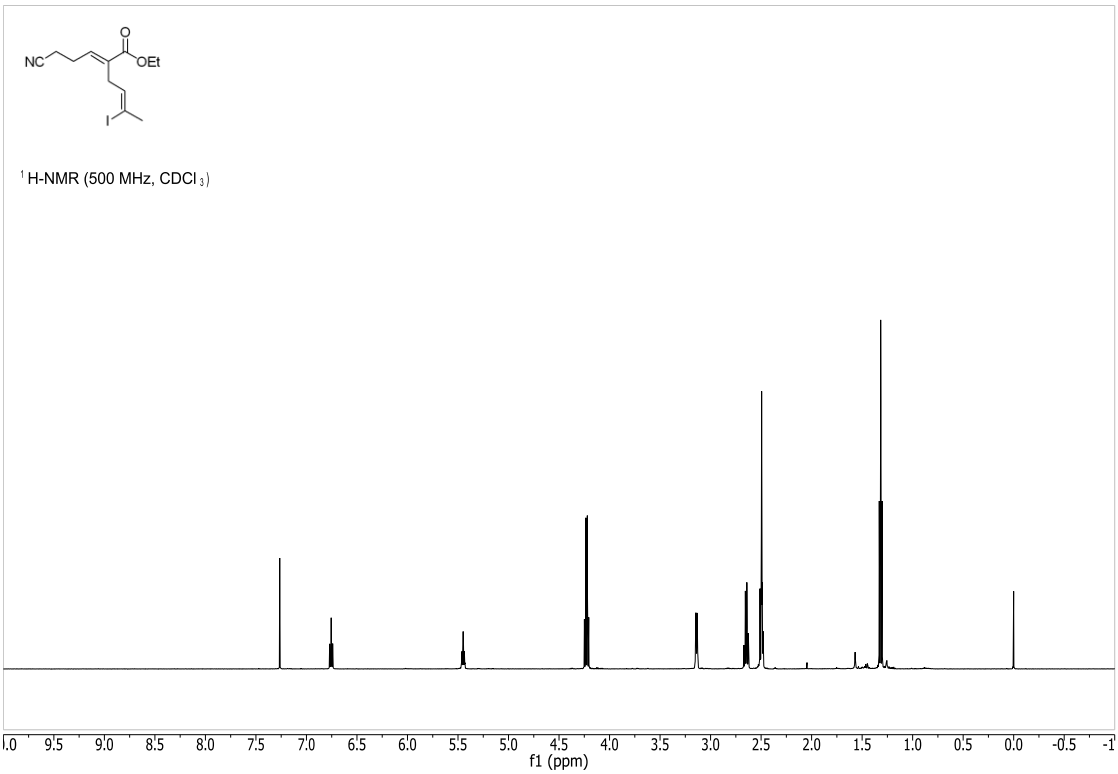
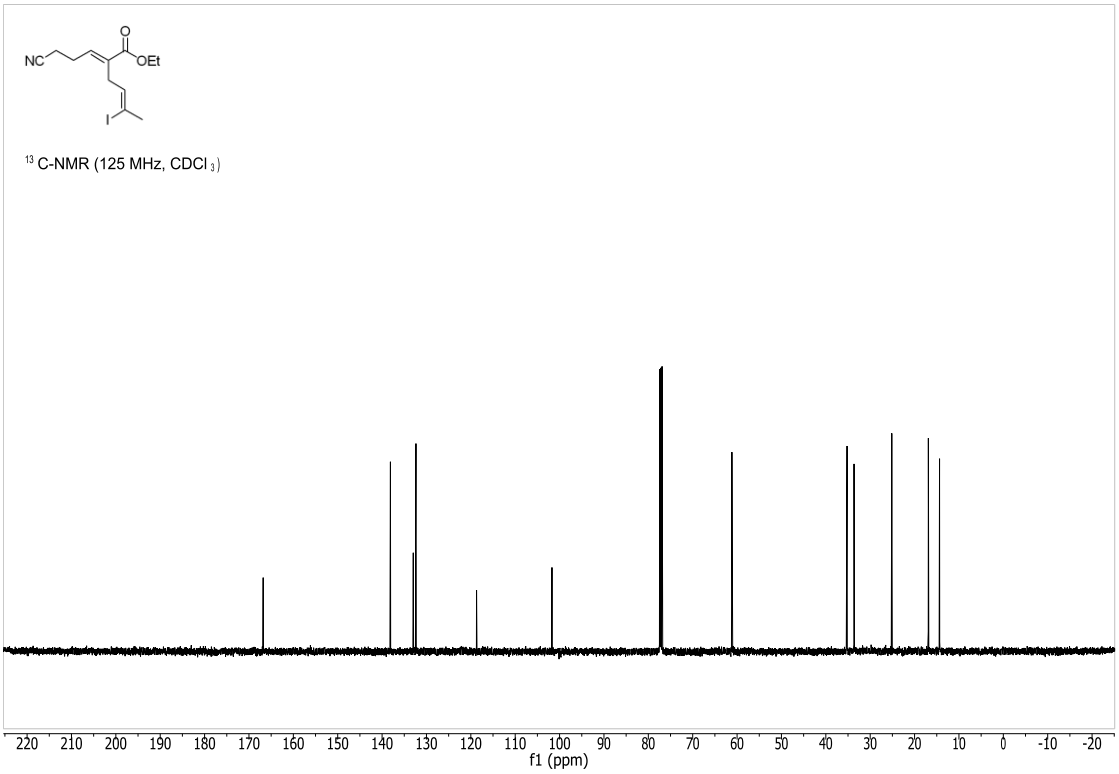

OMe
H
ROESY
f1 (ppm)
f2 (ppm)

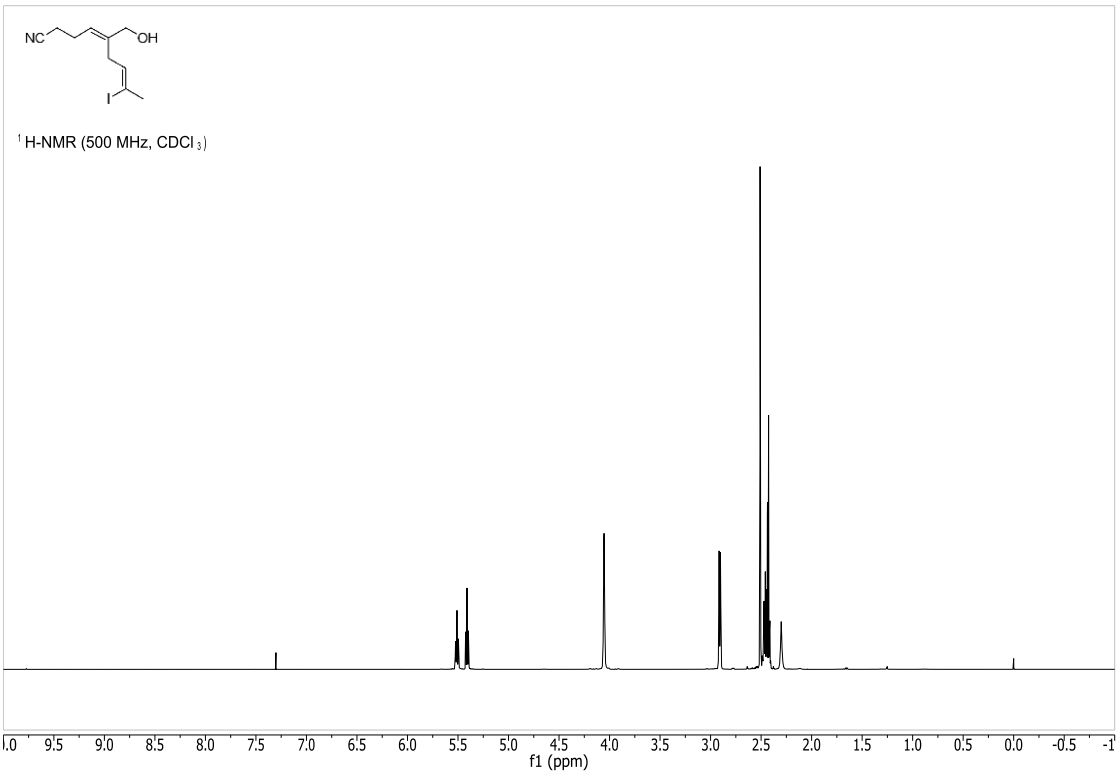
Table A1.2. 2D-NMR Data of Compound **2.21**

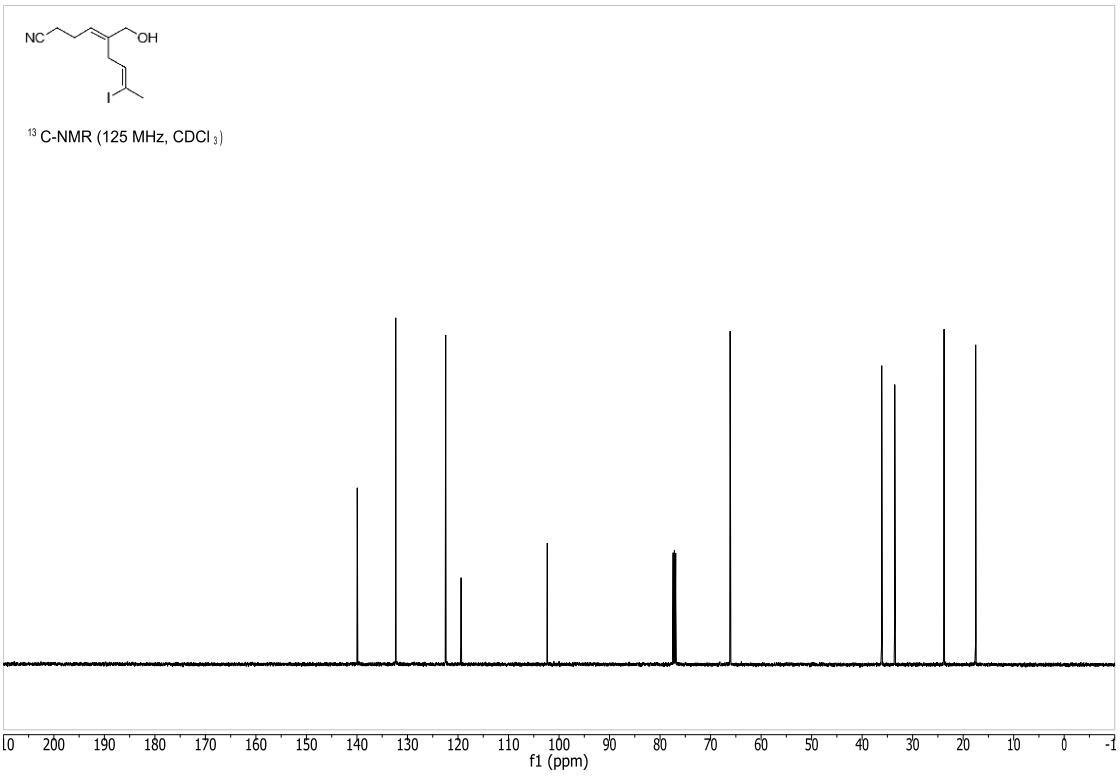


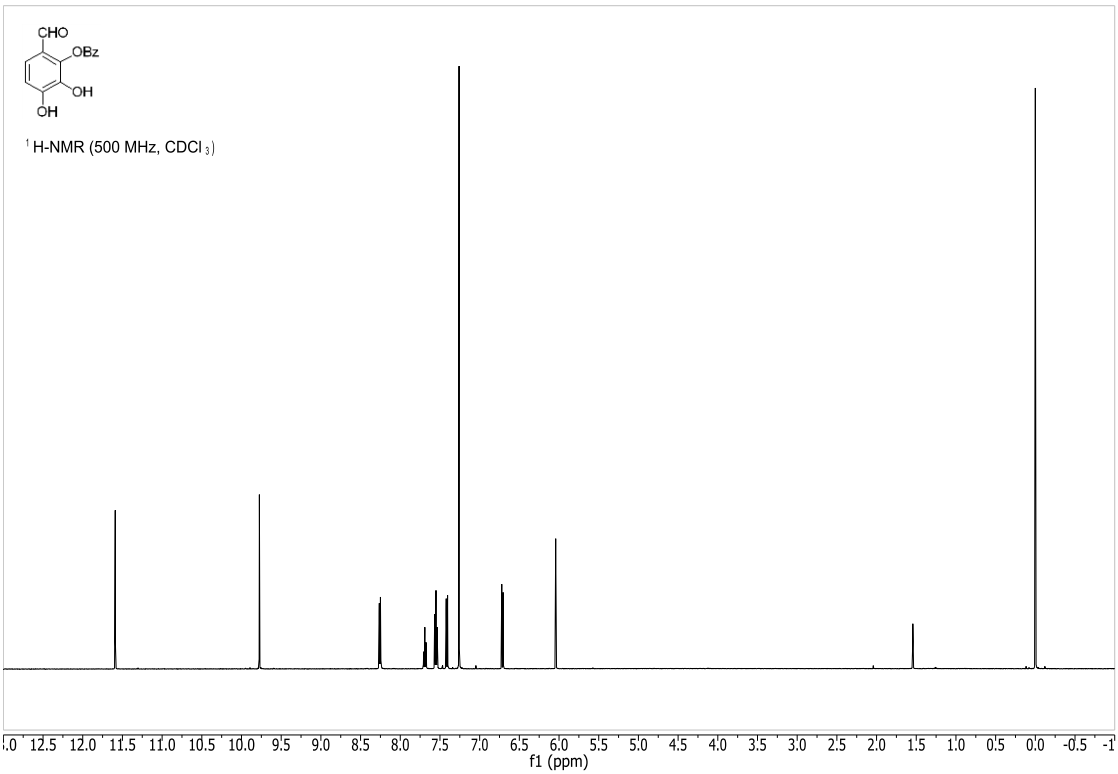
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	ROESY correlations
1	103.4		Cq			
2a	72.7	3.95	CH_2	H-2b	C-3, C-4, C-7	H-4, H-13
2b		3.67	CH_2	H-2a	C-1, C-3, C-7, C-13	H-7
3	51.7		Cq			
4	58.8	2.34	CH	H-6a	C-6, C-20, C-21	H-11, H-13, H-21a
5	49.0		Cq			
6a	31.1	2.08	CH_2		C-3, C-4, C-9	H-6b, H-10b
6b		1.88	CH_2		C-5, C-9, C-11	H-6a, H-20
7	41.8	2.46	CH	H-6b	C-9, C-10	H-2b, H-6b
8	225.0		Cq			
9	79.4		Cq			
10a	35.0	2.30	CH_2	H-10b	C-9, C-11, C-12	
10b		2.29	CH_2	H-10a	C-9, C-11, C-12	H-6a, H-11
11	45.9	1.83	CH_2		C-4, C-5, C-6, C-10, C-12, C-13	H-4, H-6a, H-10b, H-18b
12	47.8		Cq			
13	46.9	2.80	CH		C-1, C-3, C-7, C-12	H-2a, H-4, H-11, H-14
14	51.3	3.52	CH_3		C-1, C-8	H-13
15	52.8	3.46	CH_3		C-8, C-9	H-7, H-10a, H-10b
16	208.2		Cq			
17	25.0	2.18	CH_3		C-12, C-16	H-11, H-13
18a	76.7	3.28	CH_2	H-18b	C-5, C-6, C-11	
18b		3.23	CH_2	H-18a	C-4, C-5, C-11	H-11
19	59.2	3.29	CH_3		C-18	
20	132.9	5.68	CH	H-4, H-21a, H-21b	C-4, C-3, C-20	H-6b
21a	119.4	5.20	CH_2	H-20, H-21b	C-4	H-4
21b		5.16	CH_2	H-21a	C-4	

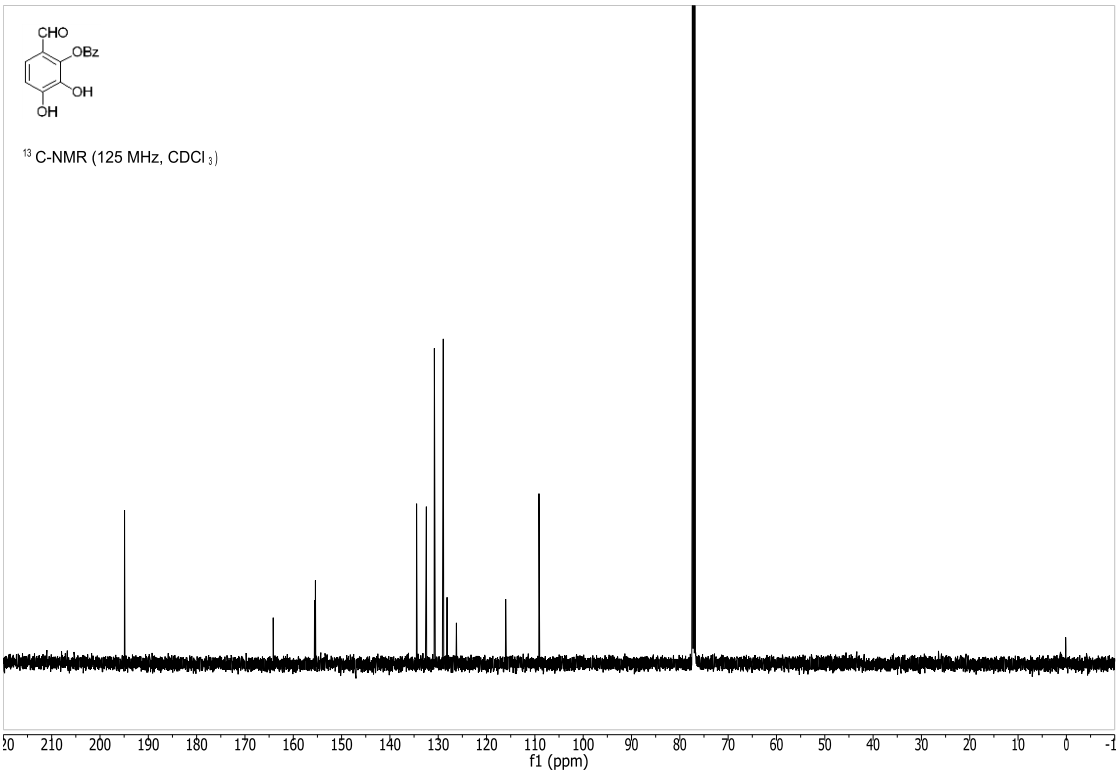

NC
O
OEt
I
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

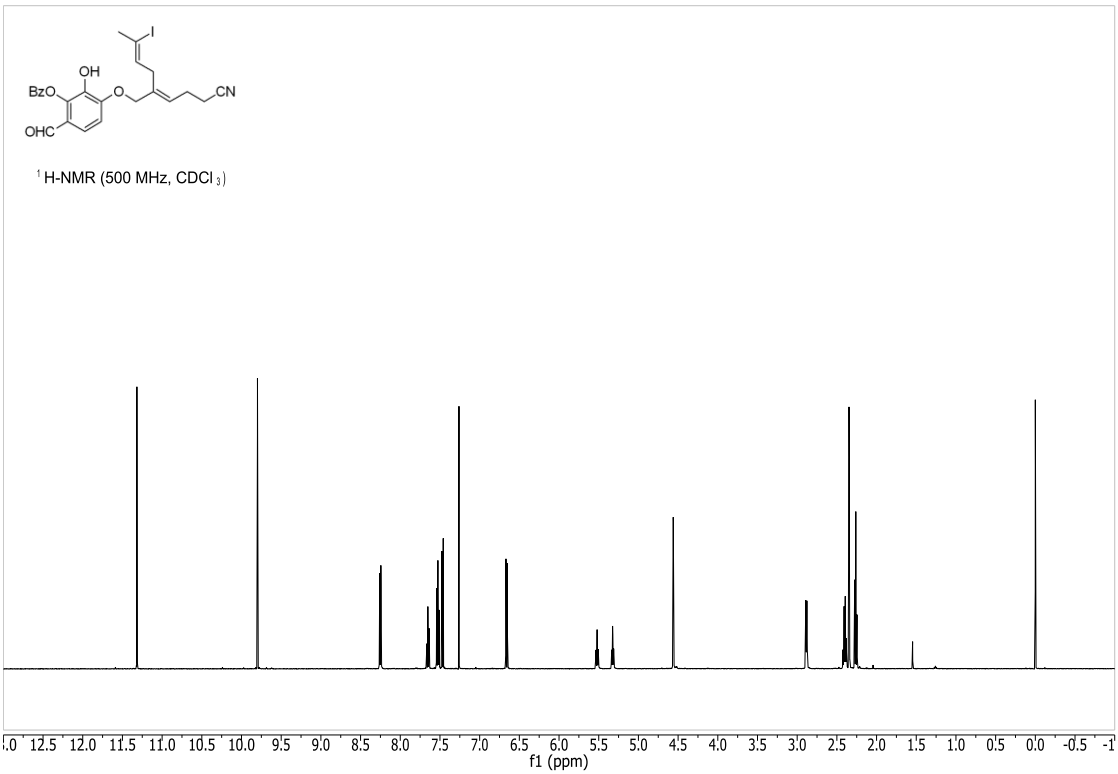

NC
O
OEt
I
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

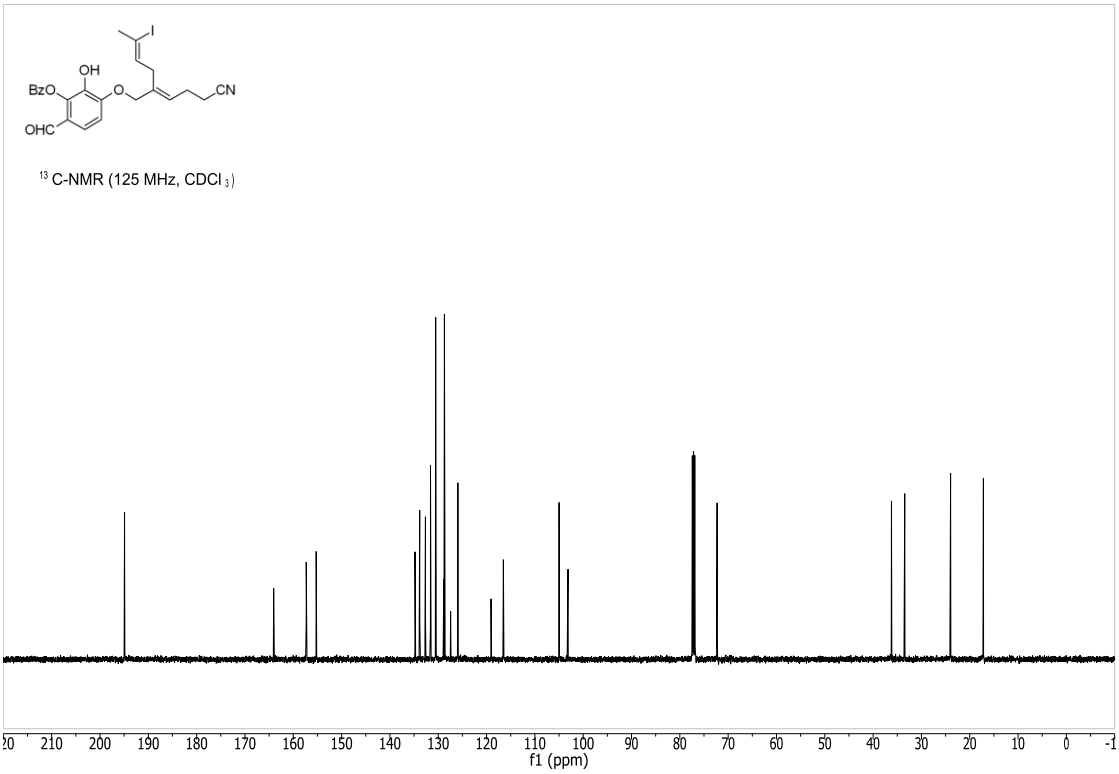

NC
OH
I
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

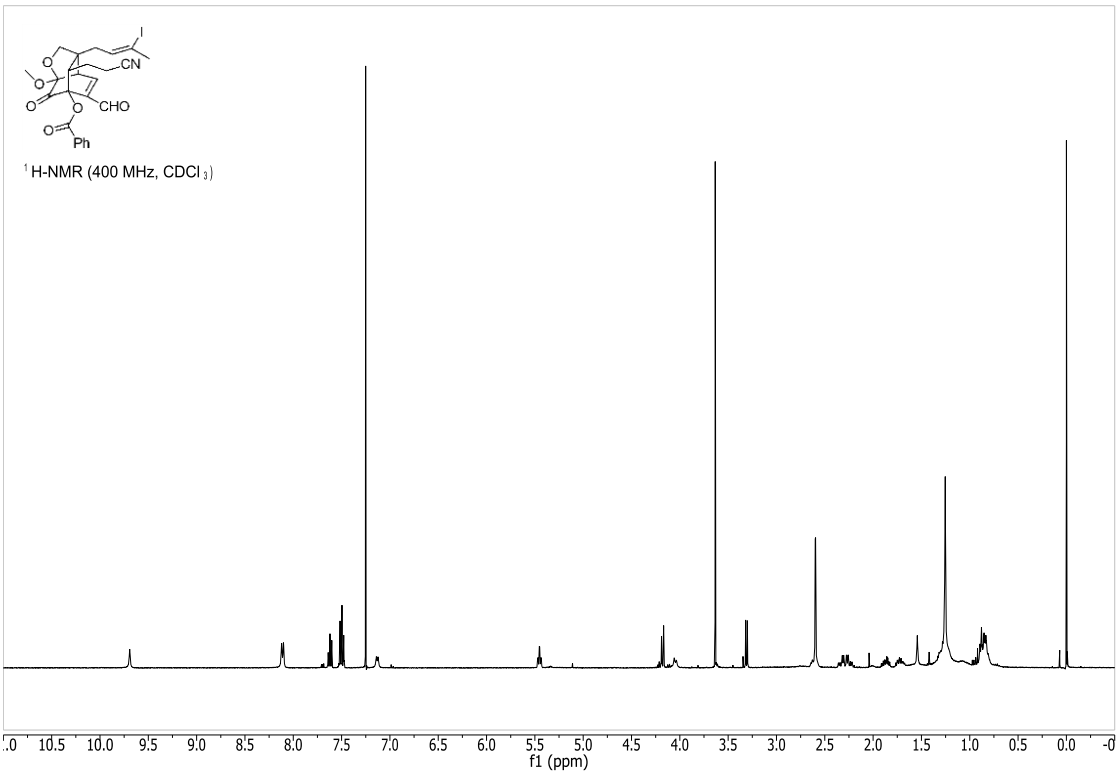

NC
OH
I
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

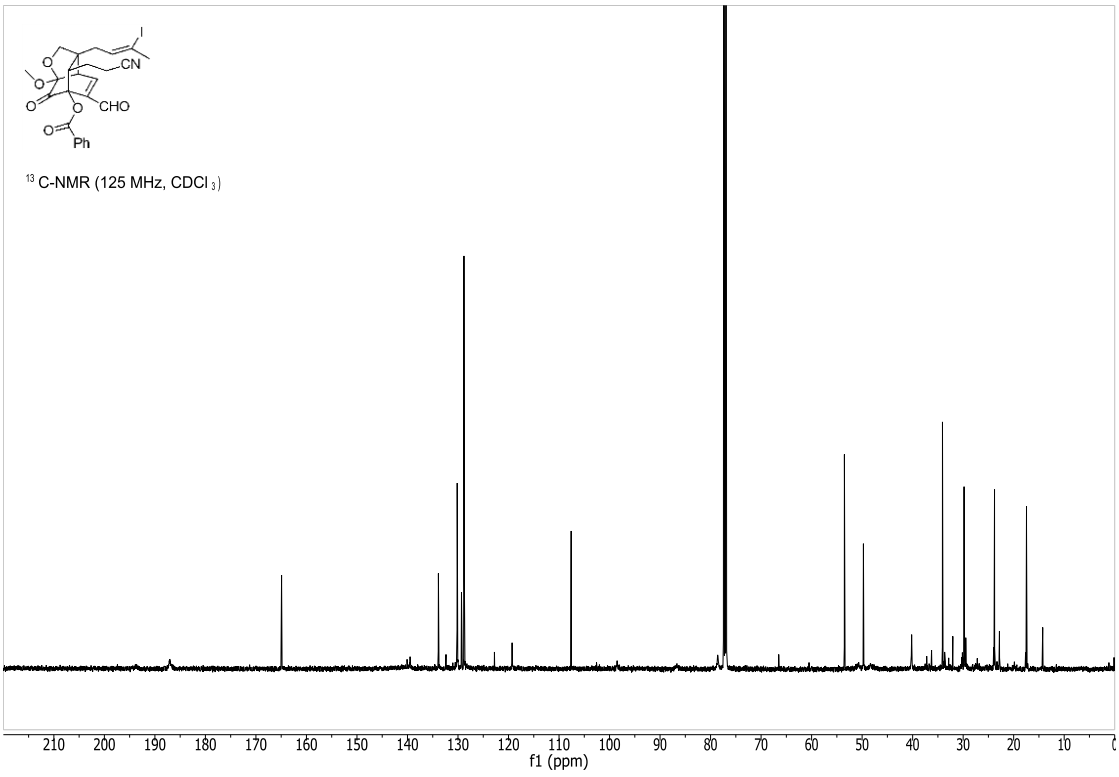

CHO
OBz
OH
OH
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

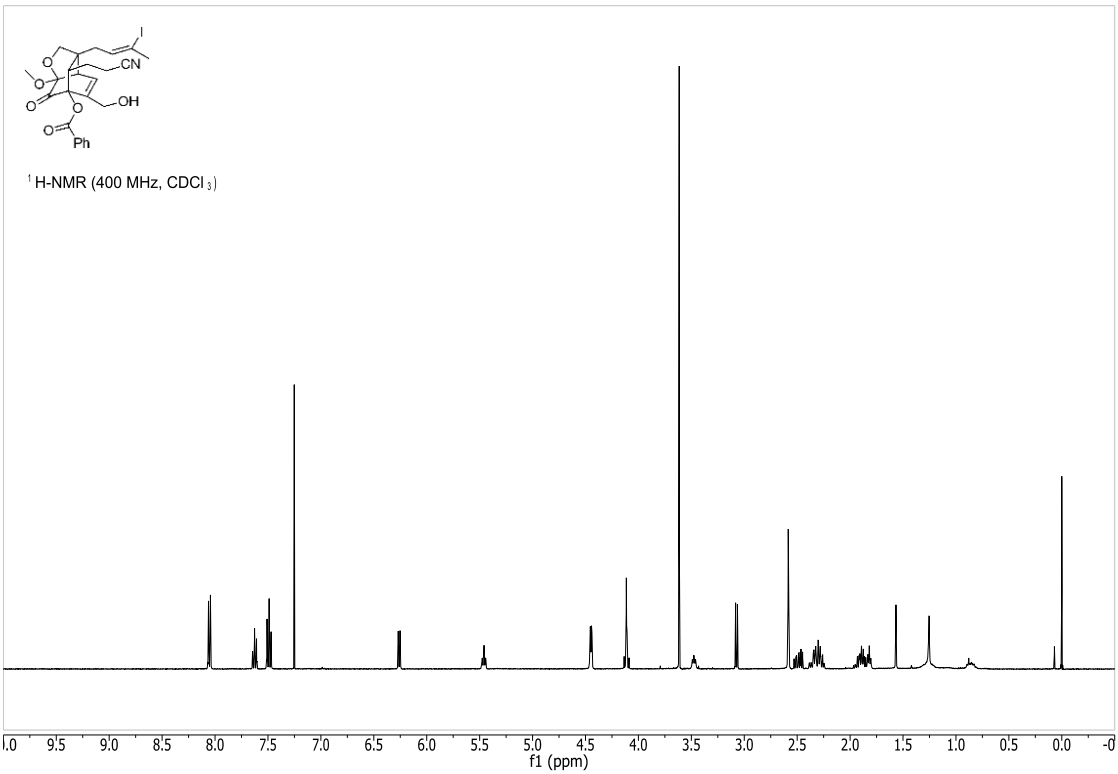

CHO
OBz
OH
OH
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

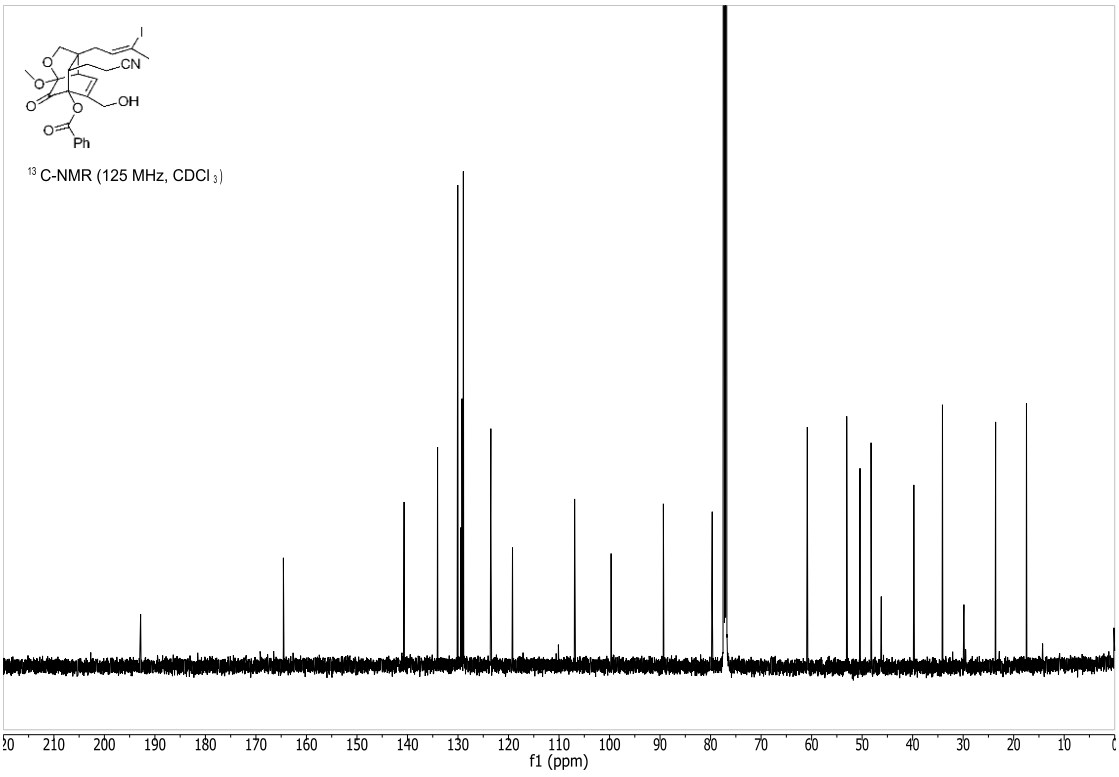

OH
BzO
O
CN
OHC
I
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

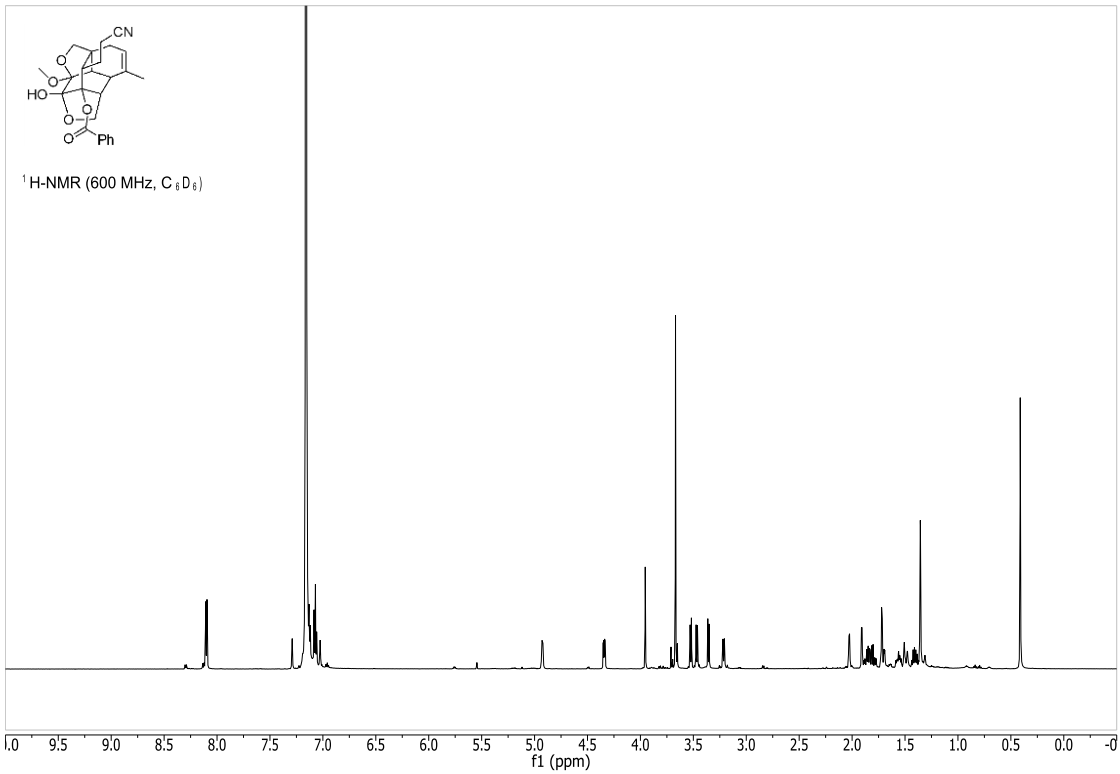

OH
BzO
O
CN
OHC
I
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

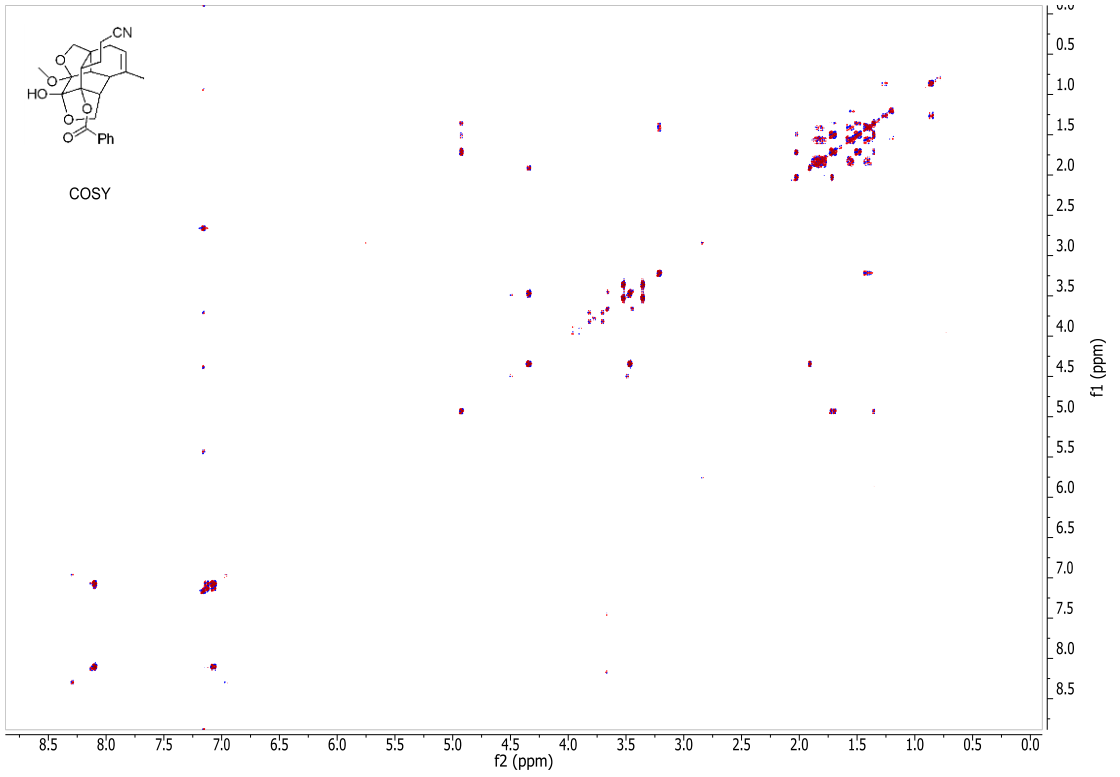

I
CN
O
O
O
CHO
O
Ph
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

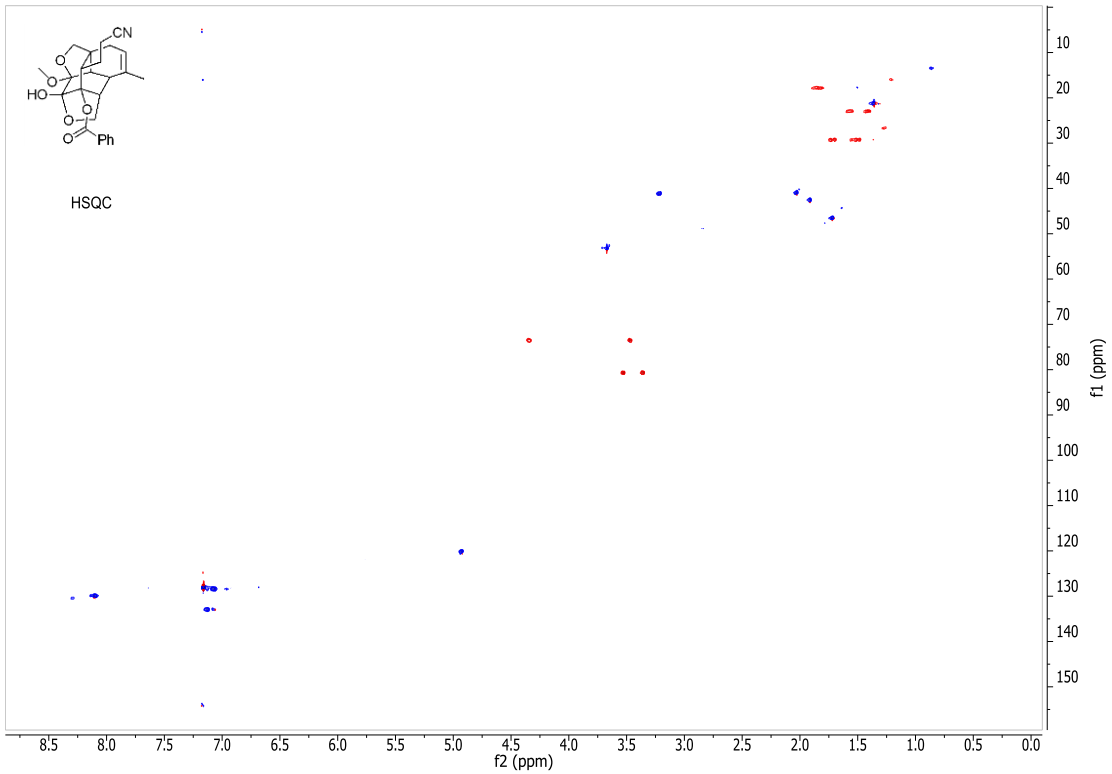

I
CN
O
O
O
CHO
O
Ph
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

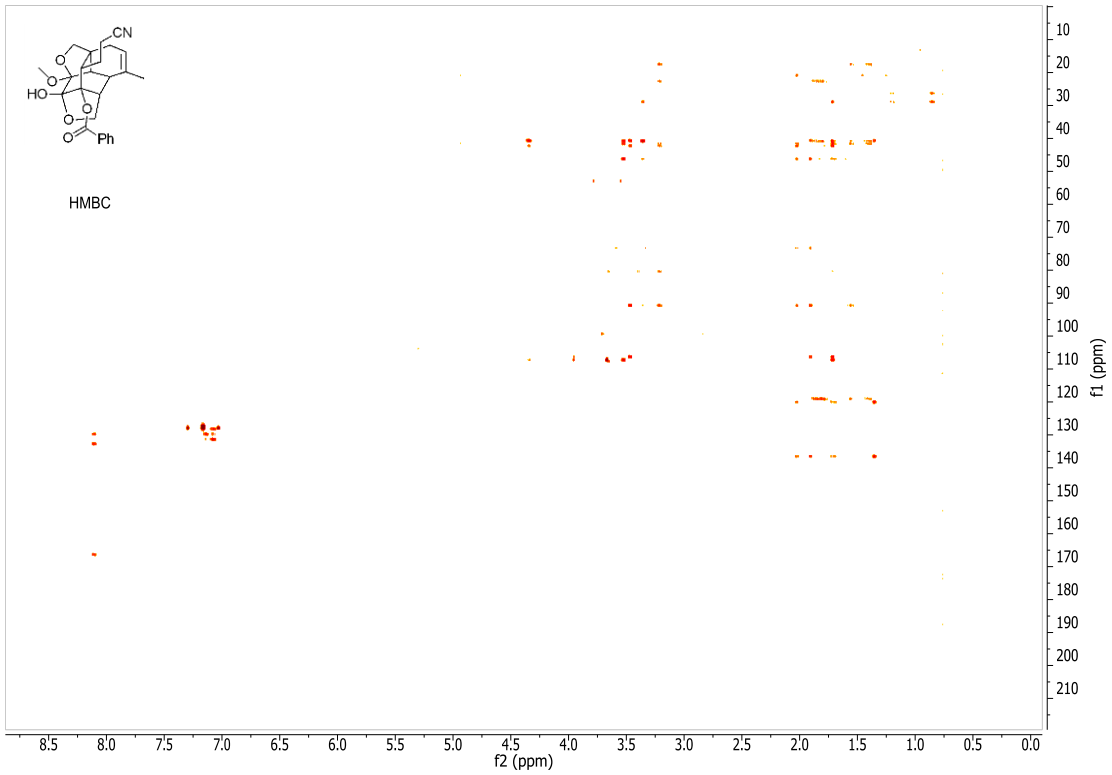

I
CN
O
O
OH
O
O
Ph
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)


I
CN
O
O
OH
O
O
Ph
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


CN
HO
O
O
O
Ph
^{1}H-NMR (600 MHz, C_6D_6)
f1 (ppm)


CN
HO
O
O
O
Ph
COSY
f2 (ppm)
f1 (ppm)


CN
HO
O
O
O
Ph
HSQC
f1 (ppm)
f2 (ppm)


CN
HO
O
O
O
Ph
HMBC
f1 (ppm)
f2 (ppm)

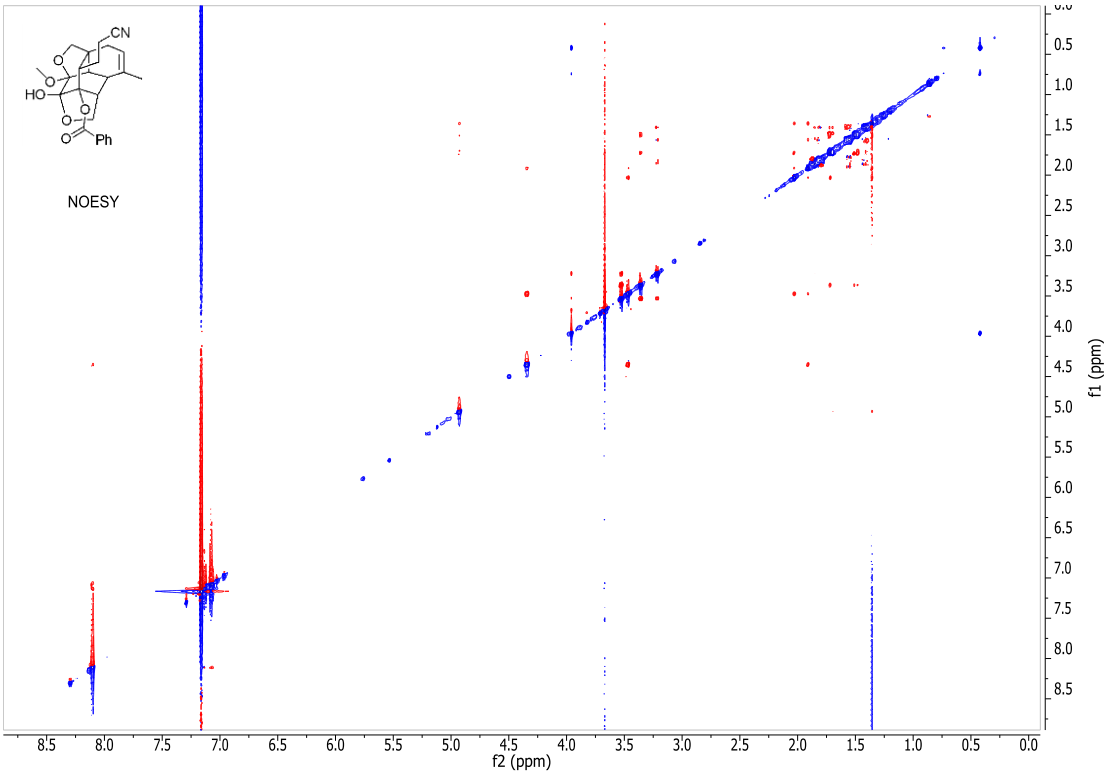
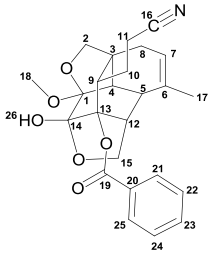
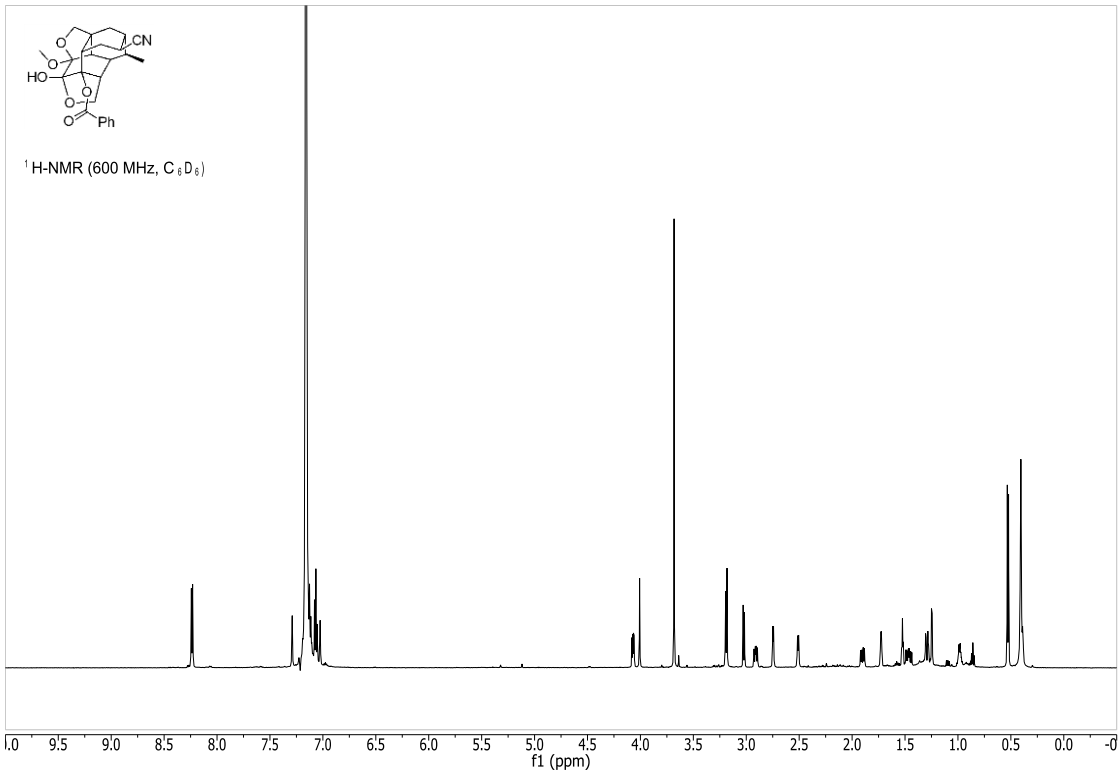


Table A1.3. 2D-NMR Data of Compound **2.35**



Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	NOESY correlations
1	107.49		Cq			
2a	80.7	3.36	CH_2	H-2b	C-14, C-13, C-4, C-9, C-8	H-2b, H-4, H-8a
2b		3.53		H-2a	C-1, C-4, C-3, C-9	H-2a, H-9
3	42.06		Cq			
4	46.51	1.72	CH	H-5	C-1, C-14, C-12, C-9, C-8	H-2a, H-8a
5	40.96	2.03	CH	H-8a, H-4	C-7, C-13, C-15, C-4, C-12, C-3, C-17	H-15a, H-4, H-17
6	136.74		Cq			

7	120.13	4.93	CH	H-8b, H-8a, H-17	C-3, C-17	H-8b, H-8a, H-17
8a	29.31	1.5	CH_2	H-7, H-5, H-8b, H-17		H-2a, H-8b
8b		1.71		H-7, H-8a, H-17	C-7, C-4	H-7
9	41.12	3.22	CH	H-10a	C-13, C-2, C-12, C-3, C-10, C-11	H-26, H-11a, H-11b, H-10a
10a	22.98	1.41	CH_2	H-9, H-11a, H-11b, H-10b	C16, C-3, C-9, C-11	H-10b
10b		1.57		H-9, H-11a, H-11b, H-10a	C16, C-13, C-3, C-9, C-11	H-9, H-10a
11a	17.81	1.82	CH_2	H-10a, H-10b	C-16, C-9, C-10	H-9
11b		1.85		H-10a, H-10b	C-16, C-9, C-10	H-9
12	42.55	1.91	CH	H-15b	C-14, C-13, C-15, C-4, C-9	H-19b, H-19a, H-17
13	91		Cq			
14	106.55		Cq			
15a	73.53	3.47	CH_2	H-15b	C-14, C-13, C-12, C-5	H-15b, H-5
15b		4.34		H-15a, H-12	C-1, C-12, C-5	H-15a, H-12
16	119.24		Cq			
17	21.2	1.36	CH_3	H-7, H-8b, H-8a	C-7, C-5	H-7
18	53.18	3.67	CH_3		C-1	
19	166.35		Cq			
20	130.02		Cq			
21	129.94	8.1	CH	H-22	C-19, C-23, C-25	H-22, H-5b
22	128.41	7.07	CH	H-21, H-23	C-20, C-24	H-21
23	132.96	7.13	CH	H-21, H-25, H-22, H-24	C-21, C-25	
24	128.41	7.07	CH			
25	129.94	8.1	CH			
26		3.96	OH		C-1, C-14	H-9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HO
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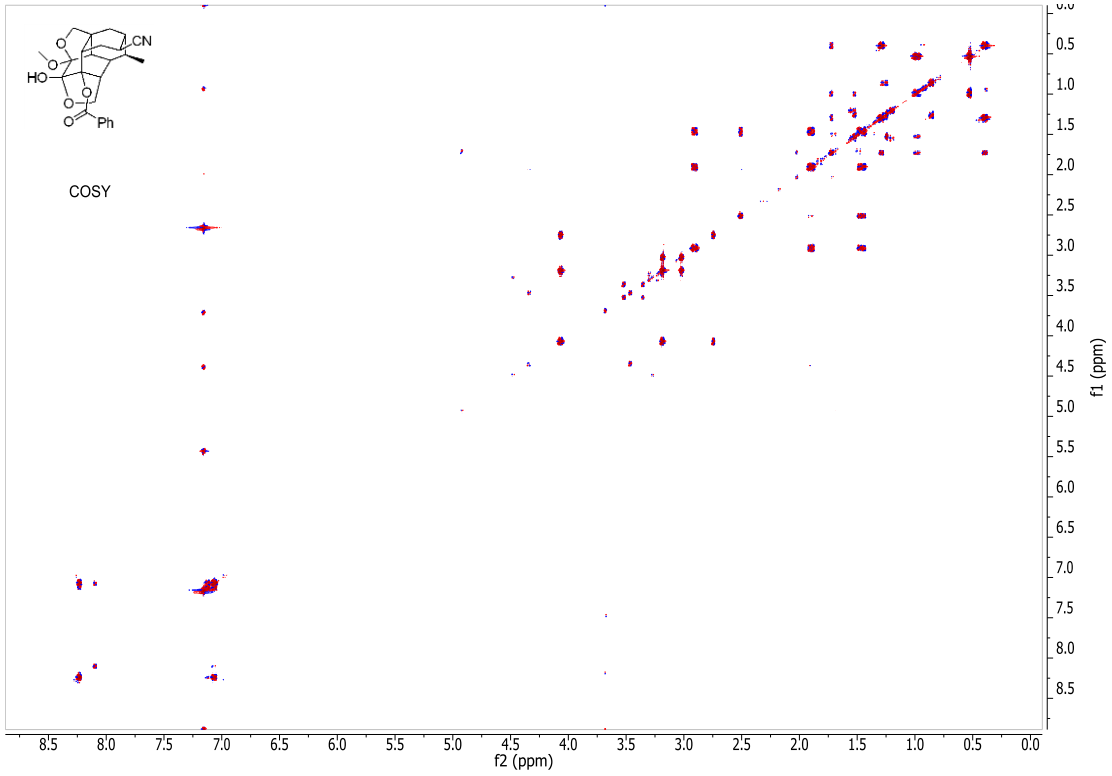
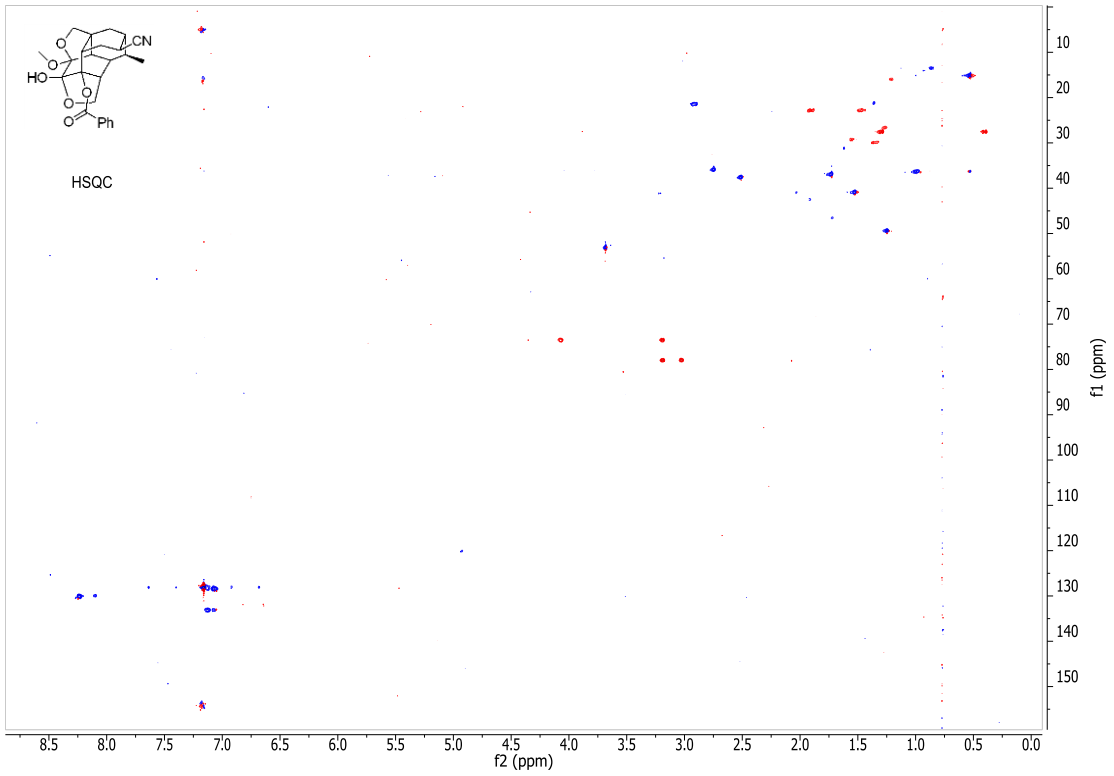
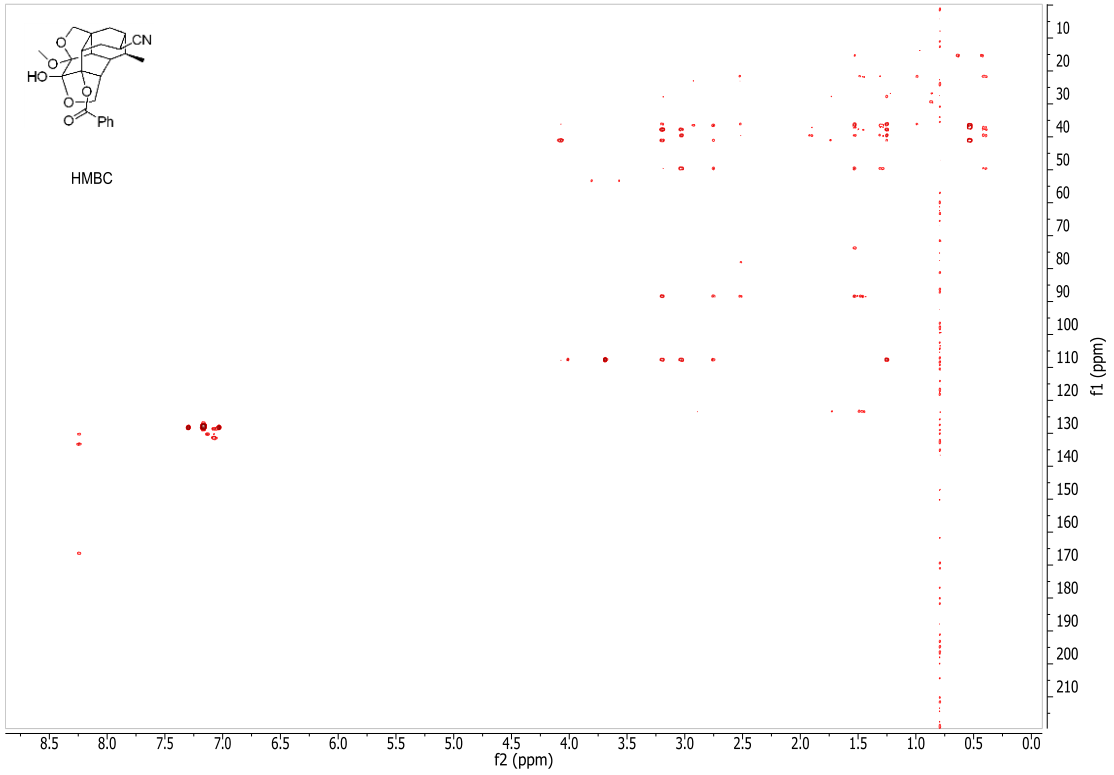
O
O
O
Ph
^{1}H-NMR (600 MHz, C_6D_6)
f1 (ppm)


CN
HO
O
O
O
O
Ph
COSY
f1 (ppm)
f2 (ppm)


HSQC
f2 (ppm)
f1 (ppm)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f1 (ppm)

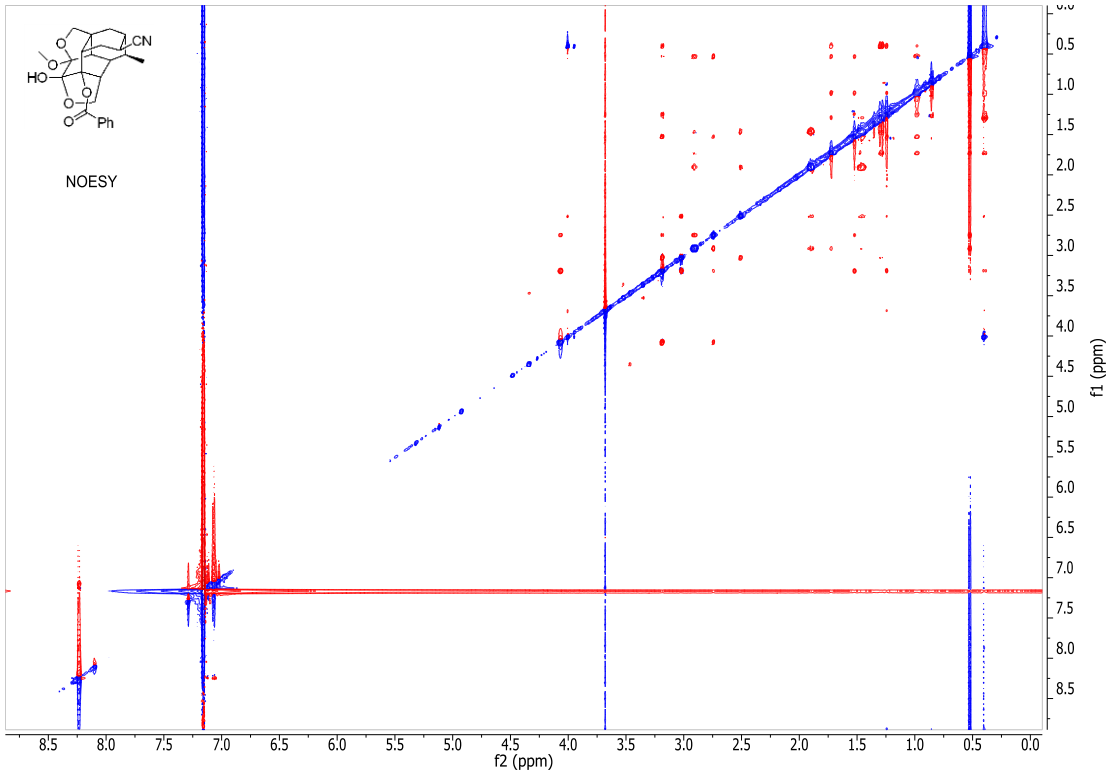
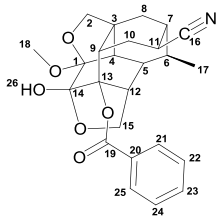
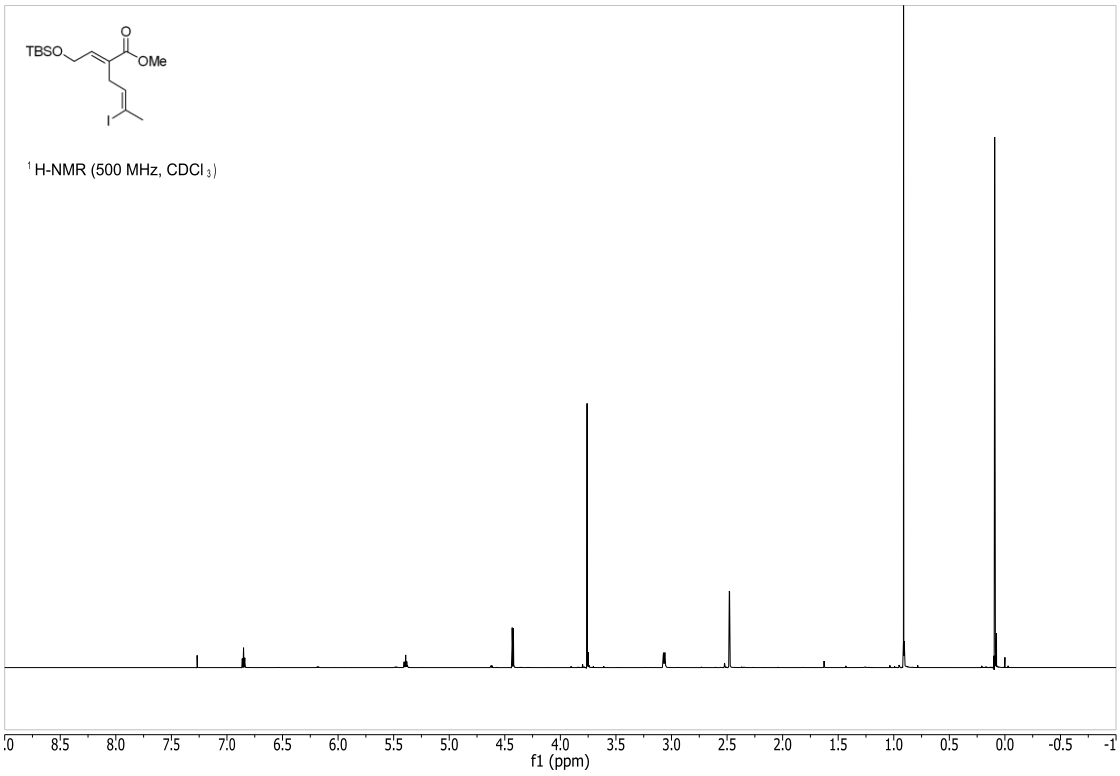


Table A1.4. 2D-NMR Data of Compound **2.36**



Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	ROESY correlations
1	107.66		Cq			
2a	78	3.02	CH_2	H-2b	C-1, C-4, C-3, C-9	H-2b, H-9, H-8b
2b		3.19		H-2a	C-1, C-9, C-8	H-2a, H-8b, H-8a
3	39.6		Cq			
4	49.39	1.25	CH	H-5	C-14, C-5, C-3, C-9, C-12, C-8	H-2b, H-5, H-6, H-8a
5	40.85	1.52	CH	H-7, H-4, H-6	C-13, C-4, C-3, C-7, C-17, C-6	H-15a, H-12, H-4, H-6, H-17
6	36.3	0.98	CH	H-7, H-5, H-17	C-12, C-11	H-7, H-5, H-4, H-17, H-8a
7	36.87	1.73	CH	H-5, H-8b, H-6, H-8a	C-16, C-5, C-3, C-6, C-8, C-10, C-11	H-11, H-8b, H-6, H-17, H-8a
8a	27.49	0.4	CH_2	H-7, H-8b	C-4, C-3, C-9, C-11, C-17	H-2b, H-7, H-8b, H-6

8b		1.29		H-7, H-8a	C-4, C-3, C-7, C-6, C-11	H-7, H-8a
9	37.58	2.5	CH	H-10b, H-10a	C-13, C-2, C-3, C-12, C-10, C-11	H-2a, H-10b, H-10a
10a	22.89	1.47	CH_2	H-11, H-9, H-10a	C-16, C-13, C-9, C-11	H-11, H-9, H-10b, H-8b
10b		1.91		H-10b, H-10a	C-3, C-9	H-11, H-9, H-10a
11	21.46	2.92	CH	H-15b	C-16, C-7, C-8, C-10	H-12, H-10b, H-10a, H-17, H-7
12	35.87	2.74	CH		C-14, C-13, C-4, C-5, C-6	H-15b, H-15a, H-11, H-5, H-17
13	88.36		Cq			
14	107.68		Cq			
15a	73.5	3.19	CH_2	H-15b	C-14, C-13, C-5, C-12	H-15b, H-12, H-5
15b		4.07		H-15a, H-12	C-4, C-5, C-12	H-15a, H-12
16	123.44		Cq			
17	15.19	0.53	CH_3	H-6	C-5, C-7	H-11, H-12, H-7, H-5, H-6
18	53.11	3.68	CH_3		C-1	H-4
19	166.34		Cq			
20	131.39		Cq			
21	130.09	8.24	CH	H-22	C-19, C-23	H-22
22	128.38	7.07	CH	H-21, H-24	C-20	H-21
23	133.15	7.12	CH	H-21, H-25, H-22, H-24	C-21	
24	128.38	7.07	CH			
25	130.09	8.24	CH			
26		4.01	OH		C-14	H-9


TBSO
O
OMe
I
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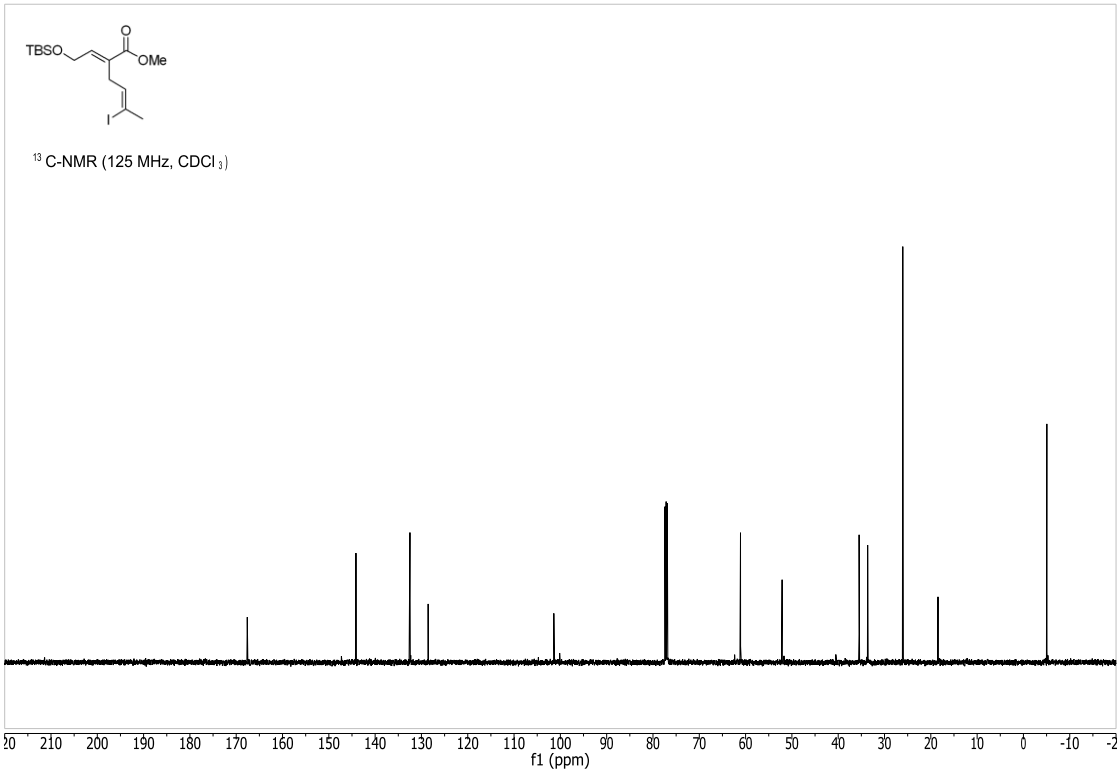
f1 (ppm)


TBSO
O
OMe
I
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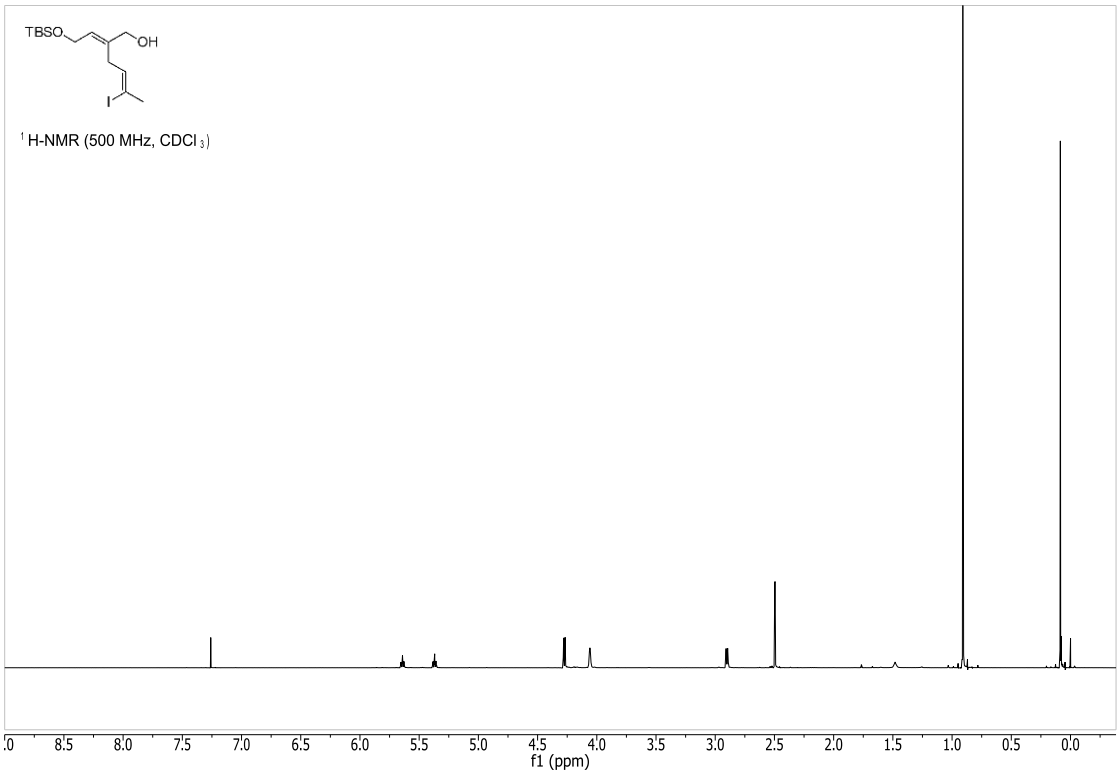
f1 (ppm)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OH
I
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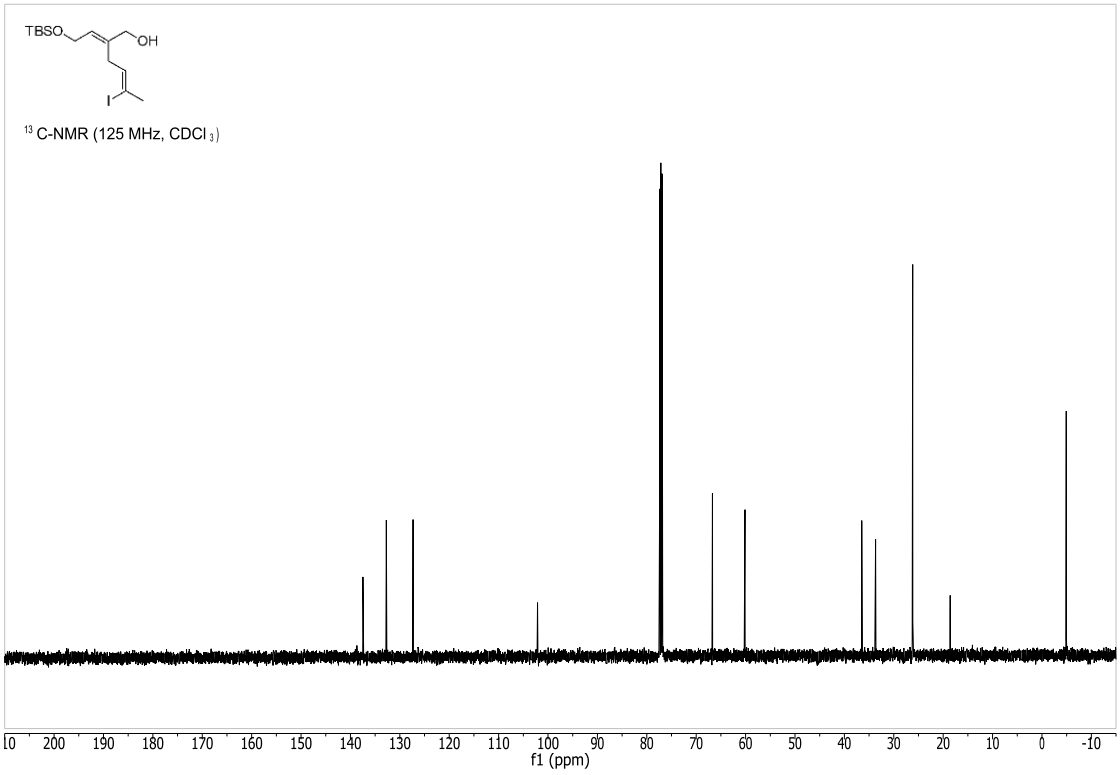
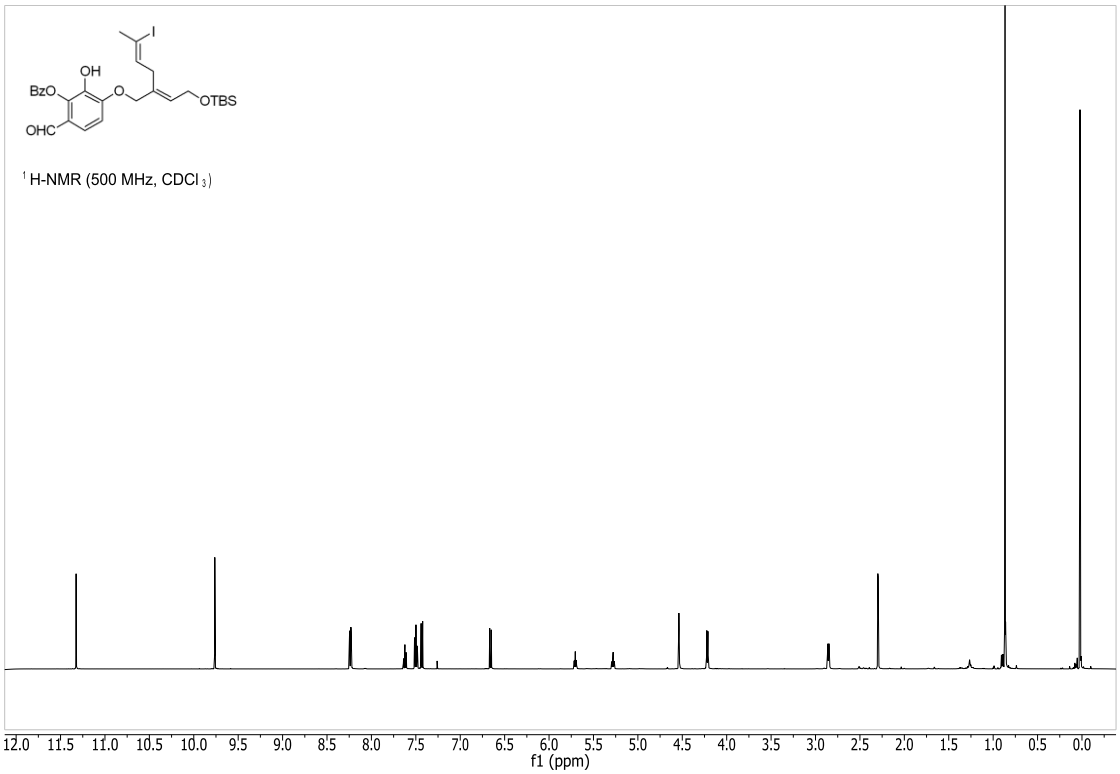
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


TBSO
OH
I
13 C-NMR (125 MHz, CDCl 3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
f1 (ppm)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BzO
O
OTBS
OHC
I
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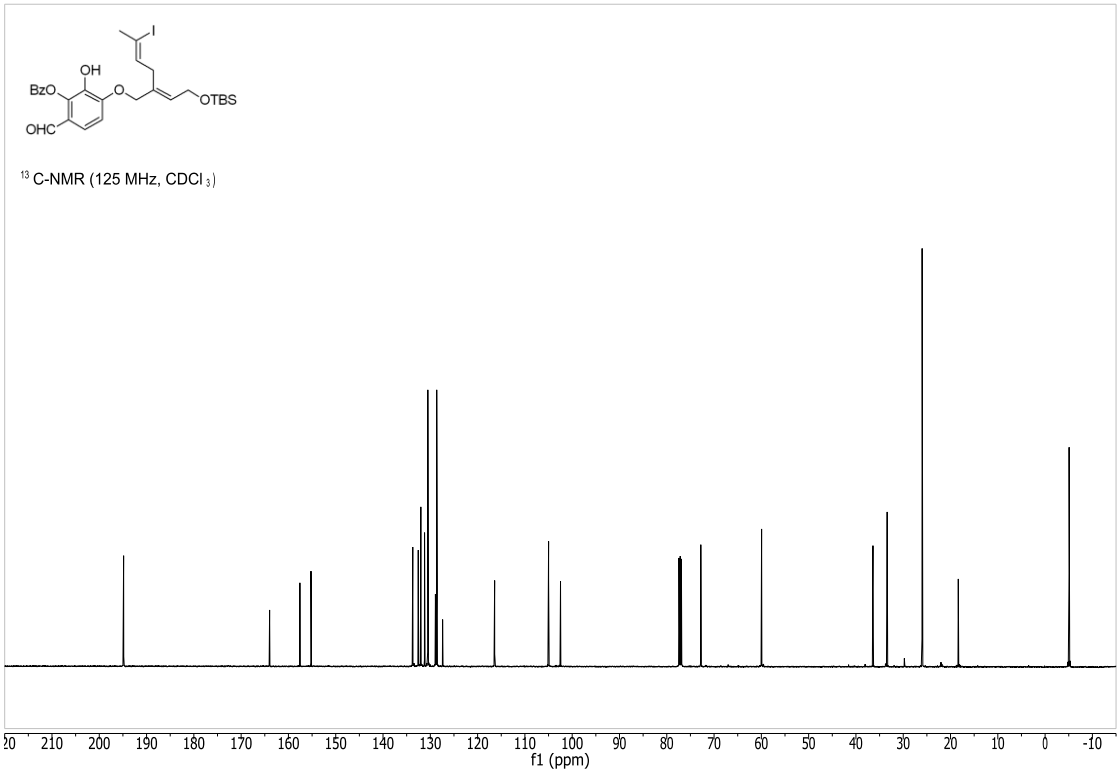
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


OH
BzO
O
OTBS
OHC
I
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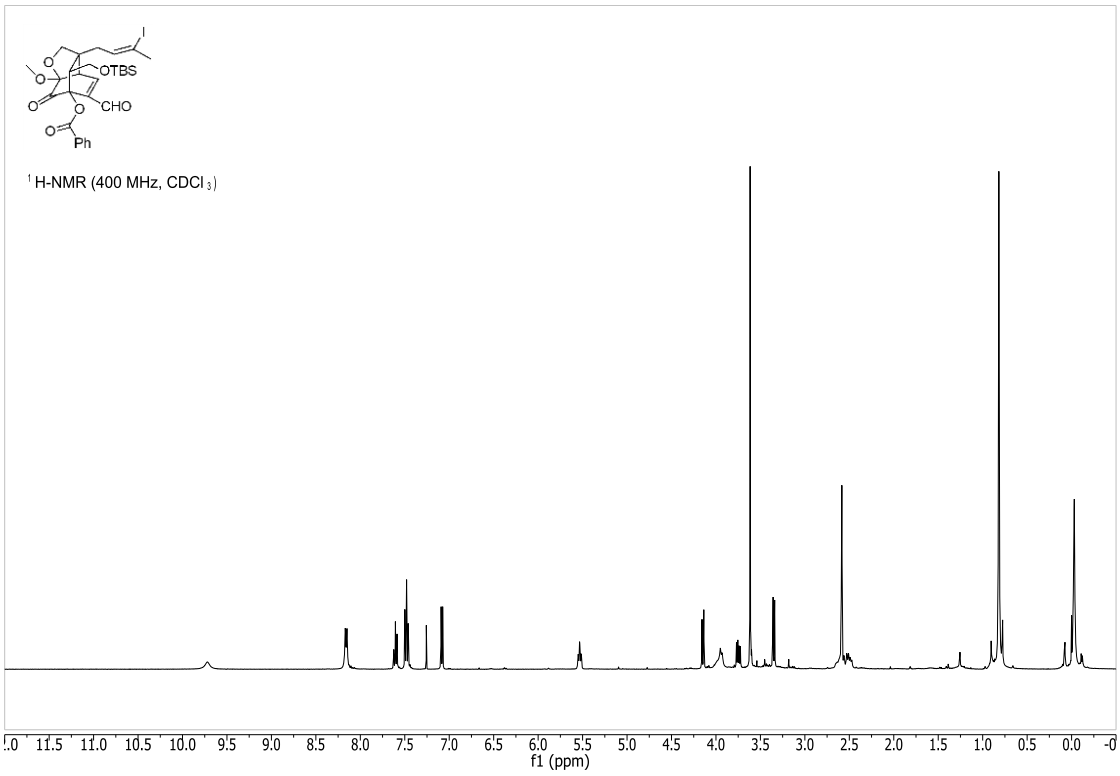
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


OTBS
CHO
Ph
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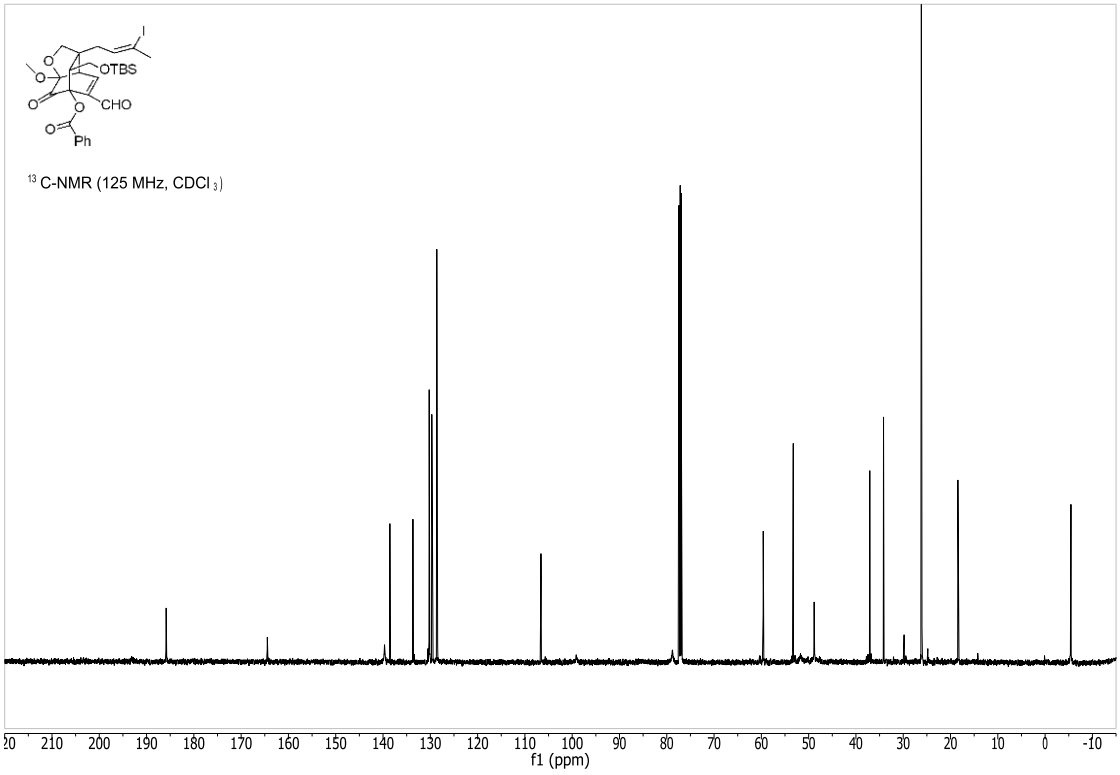
f1 (ppm)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Ph
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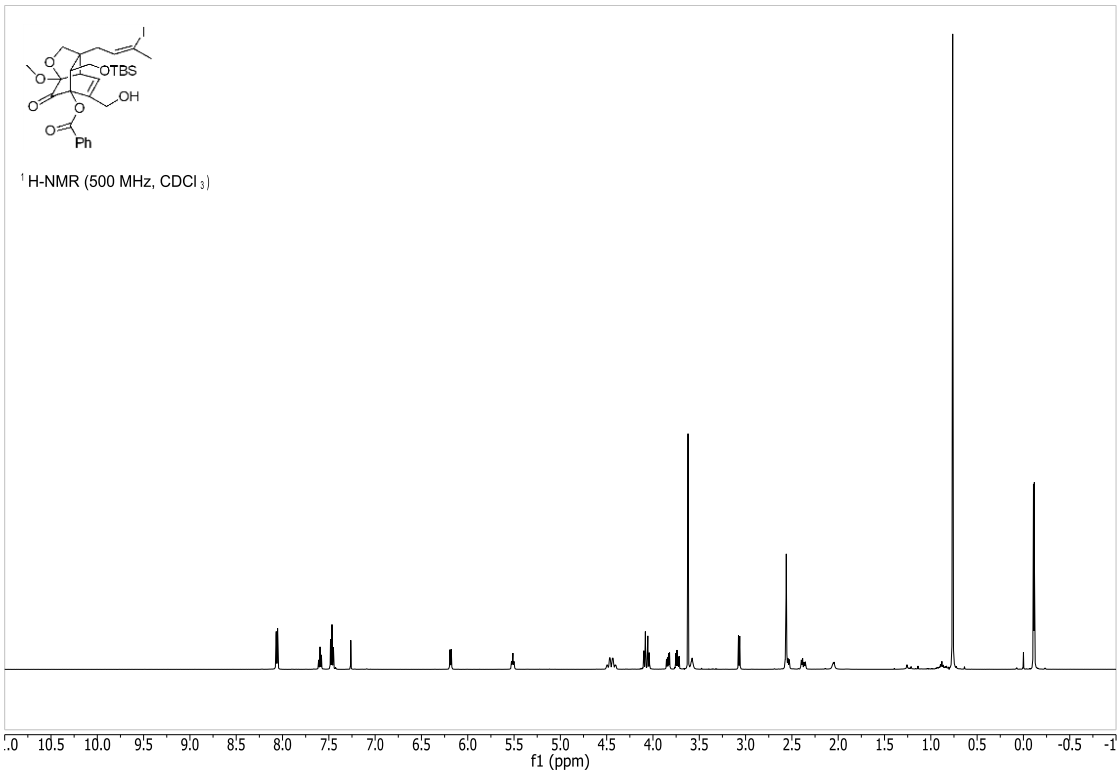
f1 (ppm)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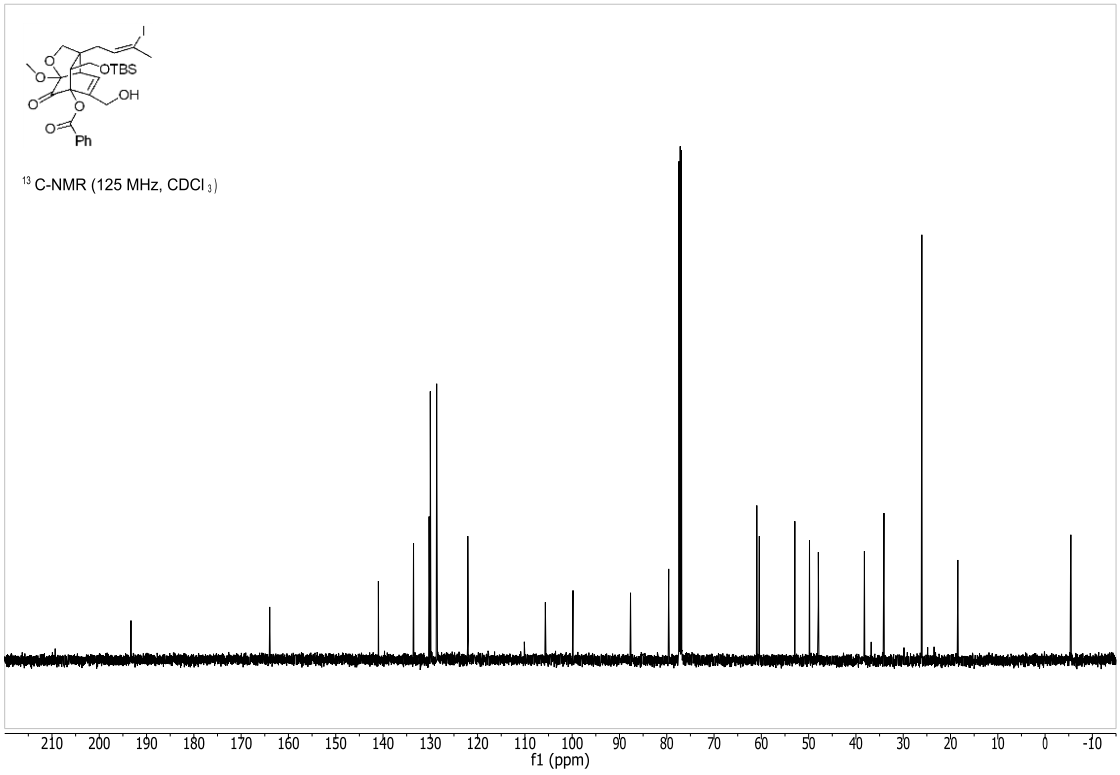
f1 (ppm)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OH
Ph
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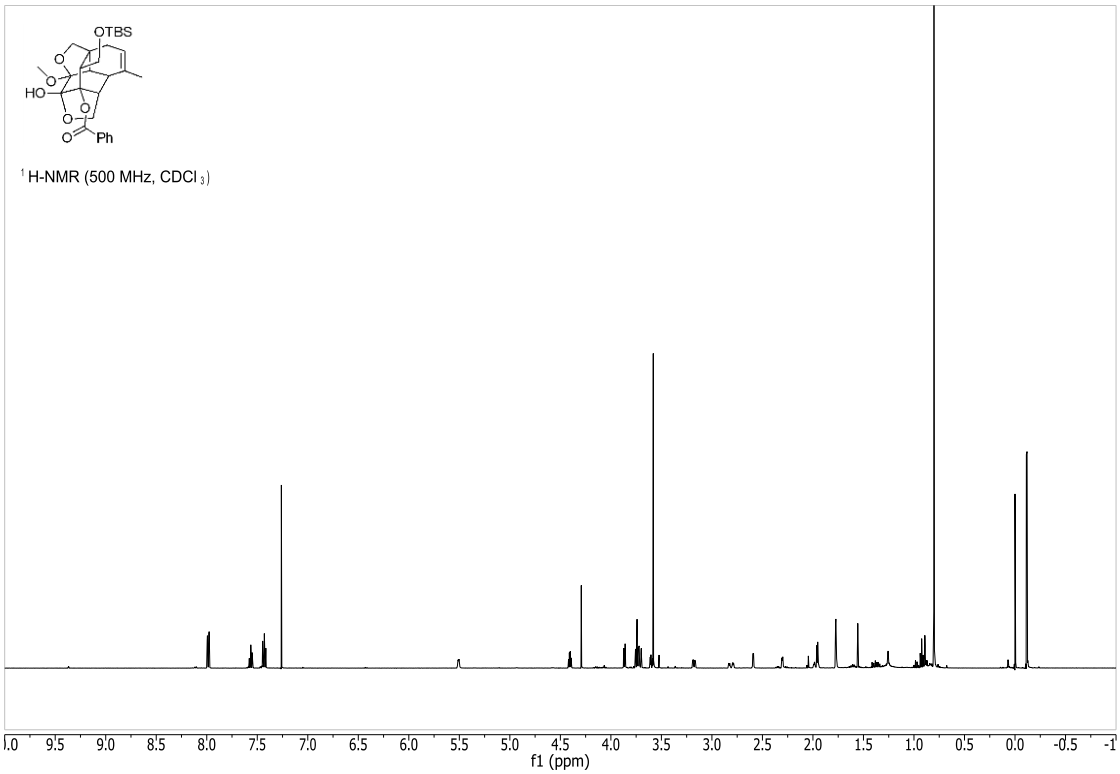
f1 (ppm)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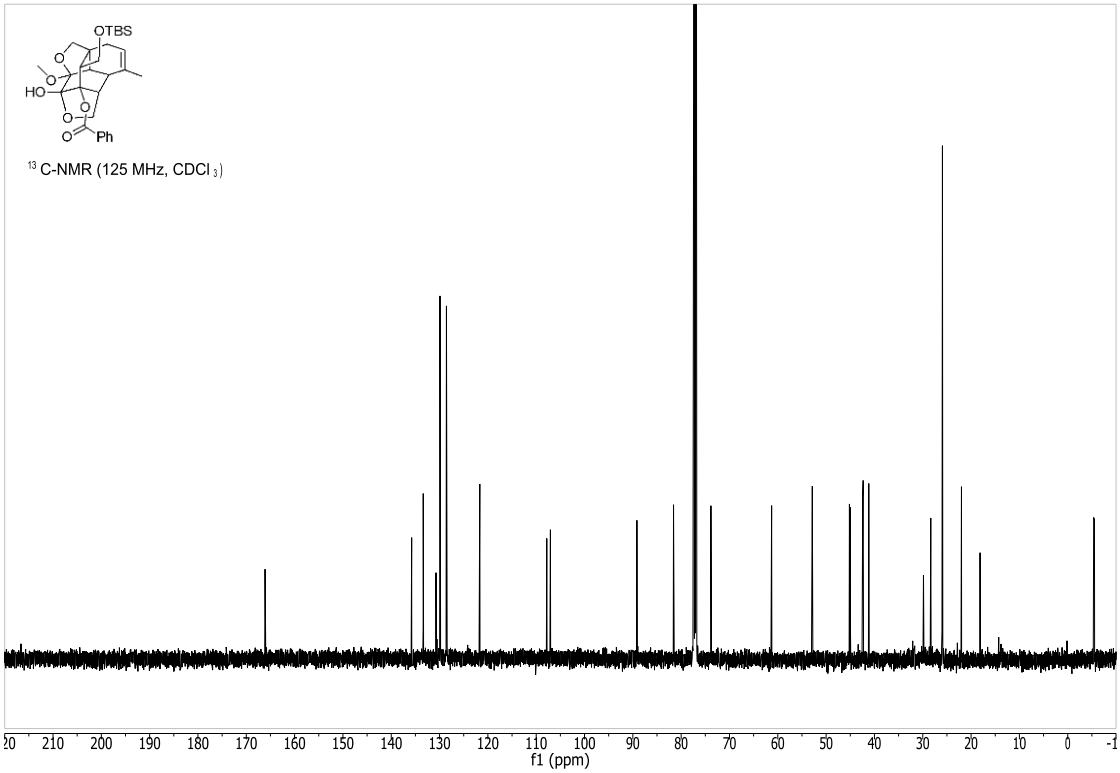
HO
O
Ph
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)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Ph
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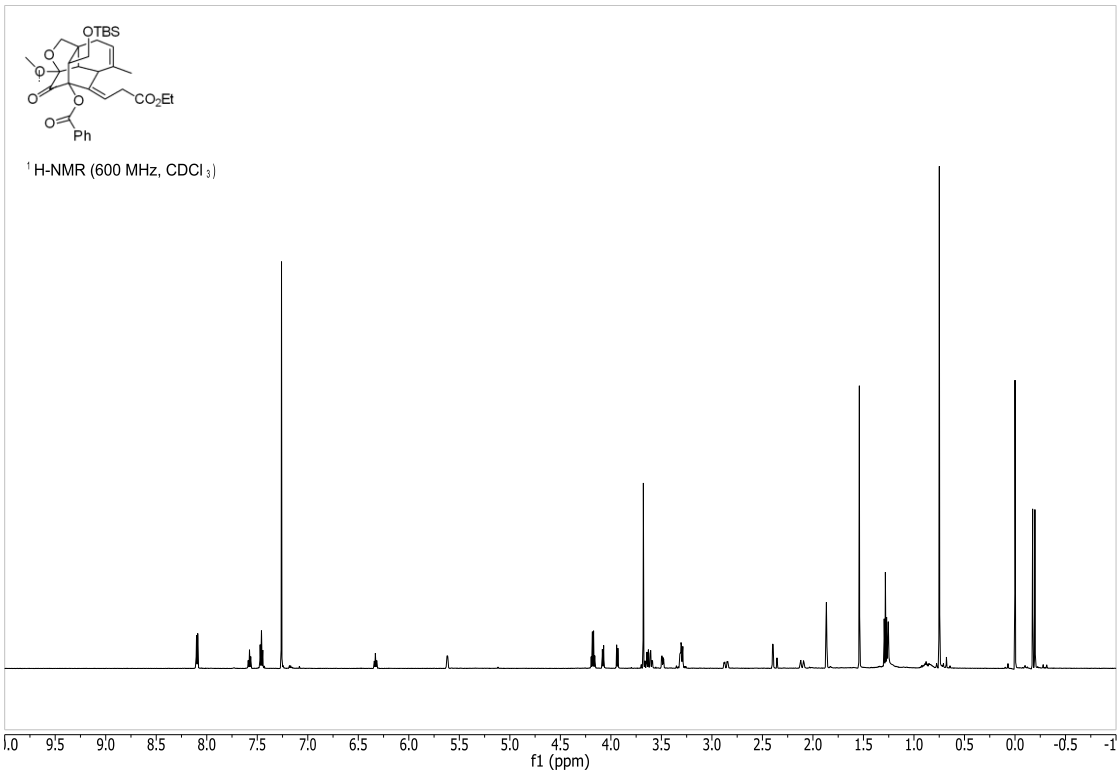
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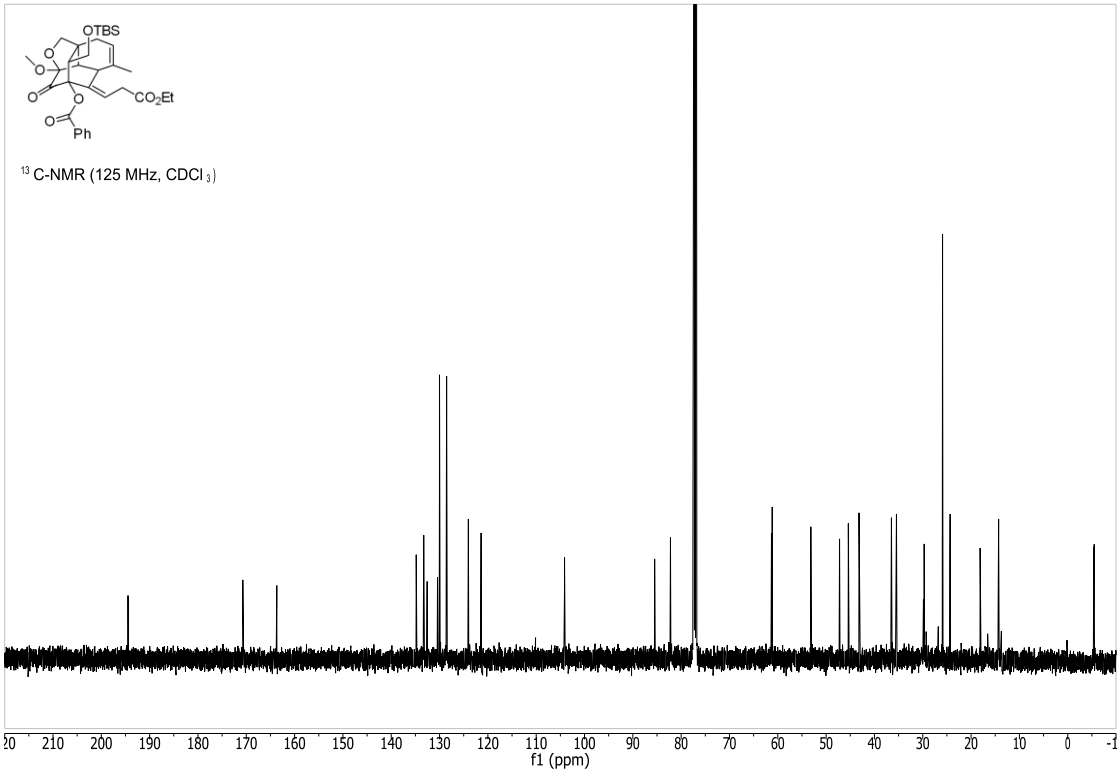
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Ph
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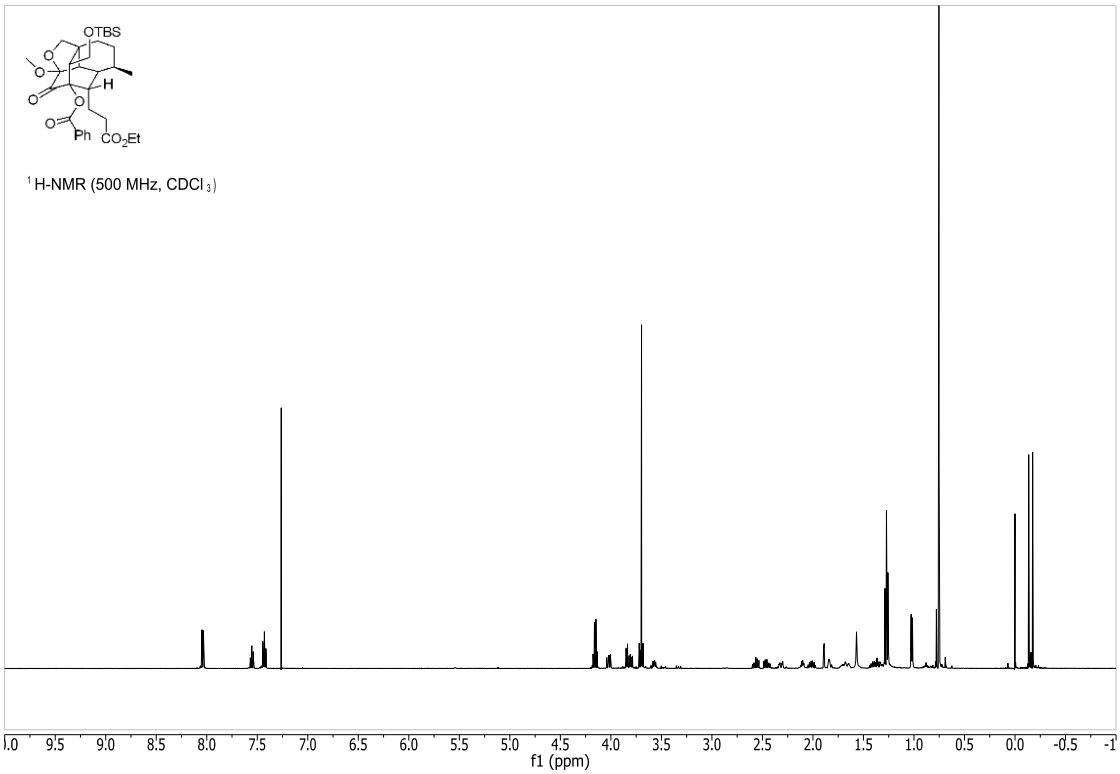
f1 (ppm)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Ph
CO2Et
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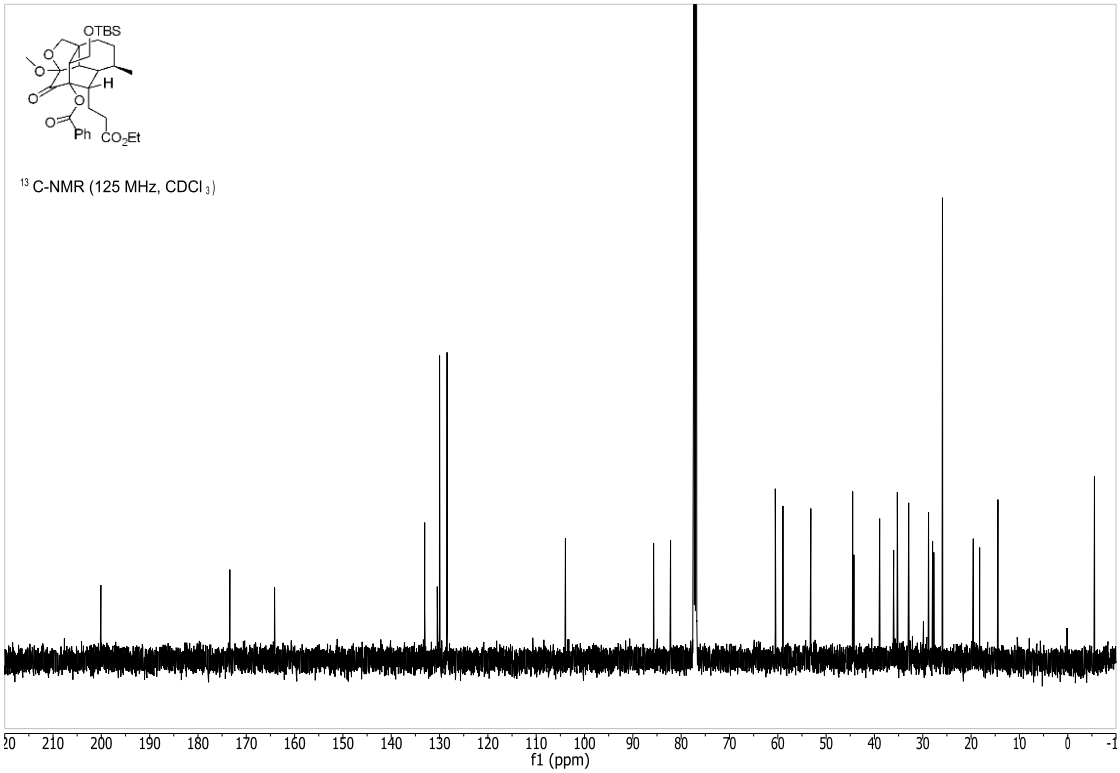
f1 (ppm)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H
Ph
CO2Et
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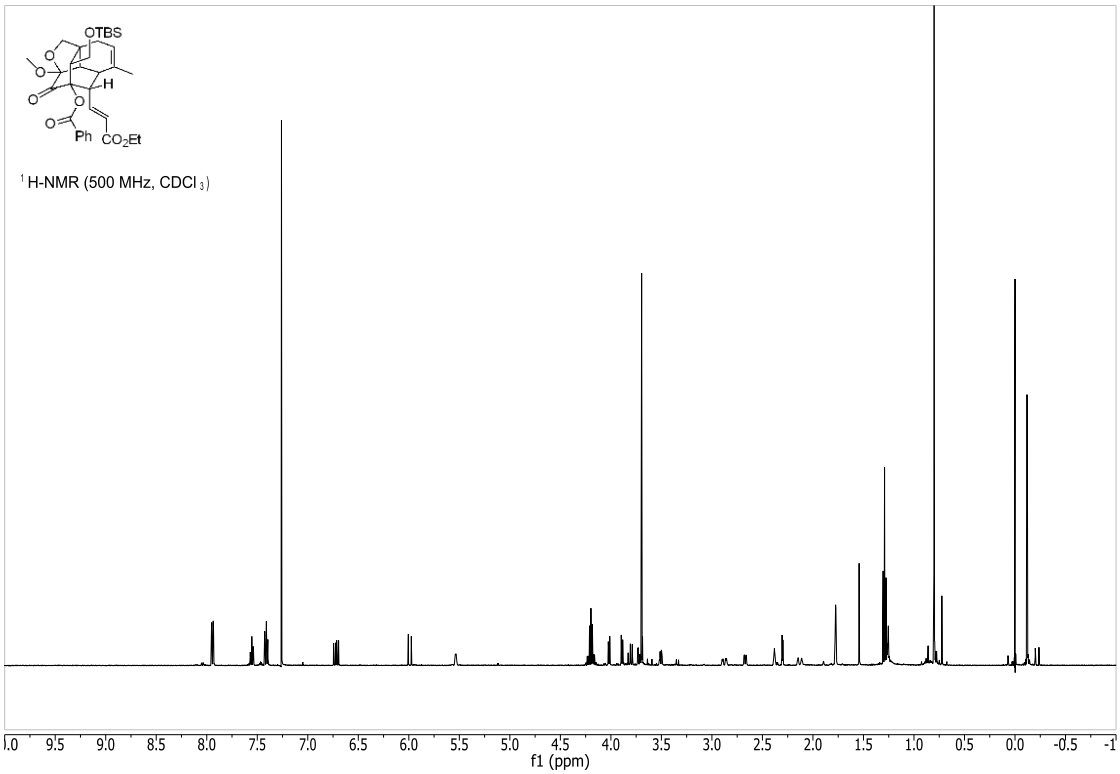
f1 (ppm)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Ph
CO2Et
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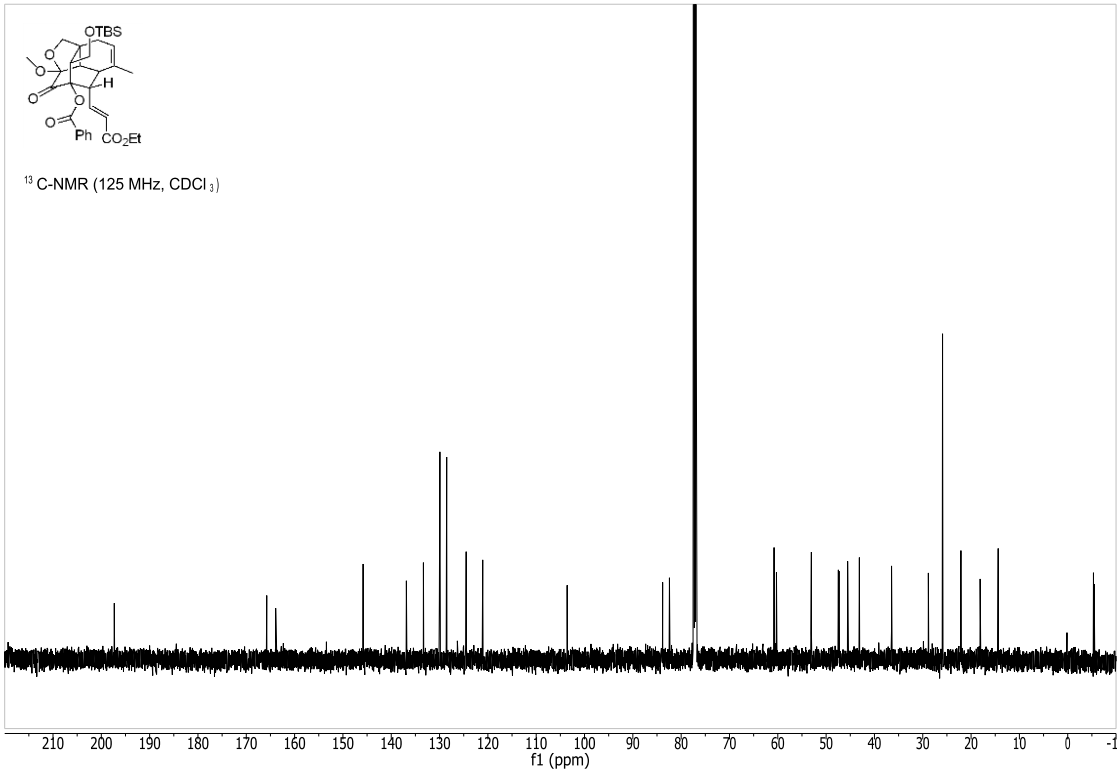
f1 (ppm)


OTBS
H
Ph
CO2Et
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

References

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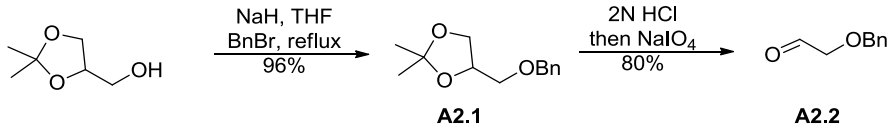
APPENDIX 2

A2.1 Experimental Procedures for Chapter 3

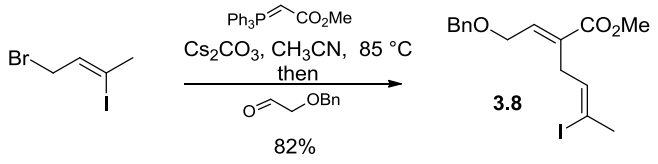


Compound **A2.2** was prepared according to literature protocol.[1]

To a suspension of sodium hydride (60 wt%, 8.04g, 201.1 mmol) in THF (600 mL) 2,3-O-isopropylideneglycerol (20.0 mL, 160.9 mmol) was added dropwise over 1 h at r.t. After stirring for 4 h, benzyl bromide (21.1 mL, 177.0 mmol) was added and the reaction mixture was heated to reflux (72 °C) for 18 h. After the reaction was cooled to r.t. and the solvent was removed, hexanes (600 mL) were added to the residue. The solid was filtered off and the filtrate was washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by column chromatography (10% ethyl acetate/hexanes) to afford a yellow oil (34.4 g, 96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.24 (m, 5H), 4.64 – 4.51 (m, 2H), 4.30 (tt, J = 6.3, 5.6 Hz, 1H), 4.06 (dd, J = 8.2, 6.3 Hz, 1H), 3.75 (dd, J = 8.2, 6.3 Hz, 1H), 3.56 (dd, J = 9.8, 5.6 Hz, 1H), 3.48 (dd, J = 9.8, 5.6 Hz, 1H), 1.42 (q, J = 0.7 Hz, 3H), 1.37 (q, J = 0.7 Hz, 3H).

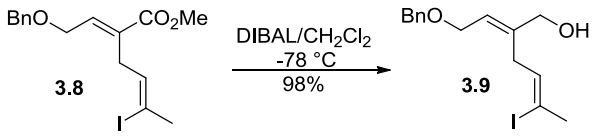
A solution of acetonide (14.6 g, 65.5 mmol) in THF (60.0 mL) was treated with 2N HCl (33.0 mL, 65.5 mmol) for 4.0 h at r.t. The reaction was concentrated, taken up in dichloromethane (180 mL) and washed with saturated $NaHCO_3$ (3 × 150

mL). The volume of the organic solution was reduced to 90 mL and sodium metaperiodate (28.0 g, 131.0 mmol) in water (180 mL) was added. The two-phase mixture was stirred at r.t. for 18 h. The organic phase was separated and the aqueous phase was extracted with dichloromethane (50 mL). The combined organic phases were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated to afford the desired aldehyde (7.83g, 80% yield), which was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (t, *J* = 0.9 Hz, 1H), 7.45 – 7.27 (m, 5H), 4.64 (s, 2H), 4.10 (d, *J* = 0.9 Hz, 2H).

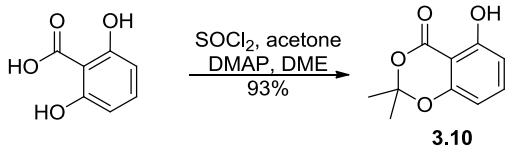


A mixture of methyl (triphenylphosphoranylidene)acetate (18.0 g, 53.8 mmol), bromide (22.1 g, 64.6 mmol) and cesium carbonate (17.5g, 53.8 mmol) in acetonitrile (225 mL) was heated at 85 °C for 5 h then aldehyde (7.61g, 50.7 mmol) in acetonitrile (25 mL) was added dropwise over 1 h. After stirring at 85 °C for 18 h the reaction was cooled to r.t. The solid was filtered off and the filtrate was concentrated. Hexanes were added to the residue and a solid crushed out, which was filtered off and washed with ethyl acetate. This operation was repeated once. The resultant filtrate was concentrated and purified by column chromatography (10% ethyl acetate/hexanes) to afford a colorless oil (16.1 g, 82% yield), which turned light brown while standing in air. ^{1}H NM R (400 MHz, $CDCl_3$) δ 7.41 – 7.26 (m, 5H), 6.93 (t, *J* = 5.9 Hz, 1H), 5.39 (tq, *J* = 6.5, 1.4 Hz, 1H), 4.55 (s, 2H), 4.29 (d, *J* = 5.9 Hz, 2H), 3.75 (s, 3H), 3.07 (d, *J* = 6.5

Hz, 2H), 2.45 (q, J = 1.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.37, 140.40, 137.81, 132.31, 130.72, 128.57 (2C) , 127.97, 127.93 (2C), 101.54, 73.01, 67.22, 52.12, 35.48, 33.58; IR (film) 2949, 2912, 2854, 1712, 1647, 1452, 1435, 1311, 1274, 1205, 1105, 1124, 1047, 738, 698 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{16}H_{20}IO_3$ $[M+H]^+$: 387.0452, found: 387.0457.

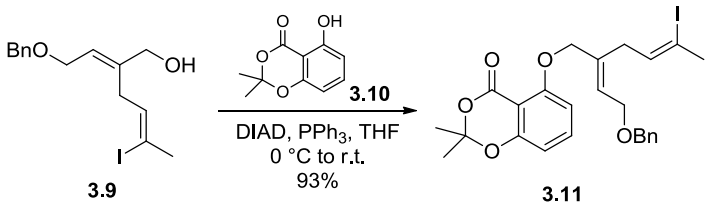


To a solution of ester (12.3 g, 31.9 mmol) in CH_2Cl_2 (250 mL) was added DIBAL (1.0 M in CH_2Cl_2, 70.2 mL) dropwise at -78 °C. The reaction was stirred at -78 °C for 5 h then quenched by 10% Rochelle's salt solution (100 mL). The mixture was warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3 × 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated to provide a colorless oil (11.2 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.25 (m, 5H), 5.73 (dddd, J = 6.6, 5.2, 1.7, 0.9 Hz, 1H), 5.35 (tq, J = 6.9, 1.4 Hz, 1H), 4.53 (s, 2H), 4.12 (dt, J = 6.6, 1.1 Hz, 2H), 4.05 (s, 2H), 2.89 (d, J = 6.9 Hz, 2H), 2.47 (q, J = 1.4 Hz, 3H), 1.79 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.54, 138.27, 132.60, 128.53 (2C), 127.97 (2C), 127.80, 123.35, 102.24, 72.66, 66.39, 66.35, 36.41, 33.61; IR (film) 3385, 2912, 2856, 1452, 1425, 1363, 1109, 1070, 1004, 736, 698 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{15}H_{19}INaO_2$ $[M+Na]^+$: 381.0322, found: 381.0316.



3.10

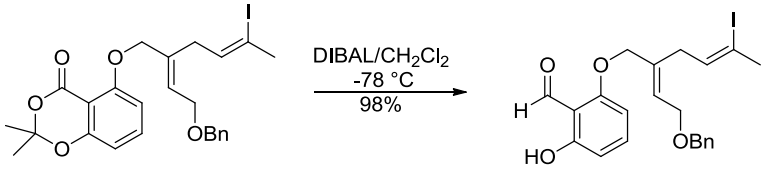
Compound **3.10** was prepared according to literature procedure.[2] A solution of 2, 6-dihydroxybenzoic acid (30.0 g, 194.6 mmol), 4-dimethylaminopyridine (1.19 g, 9.74 mmol) and acetone (18.6 mL, 252.9 mmol) in dimethoxyethane (150 mL) was cooled to 0 °C and thionyl chloride (18.4 mL, 252.9 mmol) was added dropwise. Upon completion of the addition, the resultant solution was allowed to stir at 0 °C for 1 h then r.t. 20 h. The reaction solution turned from light yellow to brown to red over time. The reaction was then cooled to 0°C, quenched by slow addition of saturated $NaHCO_3$ (100 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The resultant solid was triturated with hexanes and collect by vacuum filtration to afford a light yellow solid (32.0 g, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$) d 10.34 (s, 1H), 7.41 (t, J = 8.3 Hz, 1H), 6.64 (dd, J = 8.5, 1.0 Hz, 1H), 6.44 (dd, J = 8.1, 0.9 Hz, 1H), 1.75 (s, 6H).



3.9 **3.11**

To a solution of alcohol (5.30 g, 14.8 mmol), phenol (3.14 g, 17.8 mmol) and triphenylphosphine (4.67 g, 17.8 mmol) in THF (100 mL) was added diisopropyl

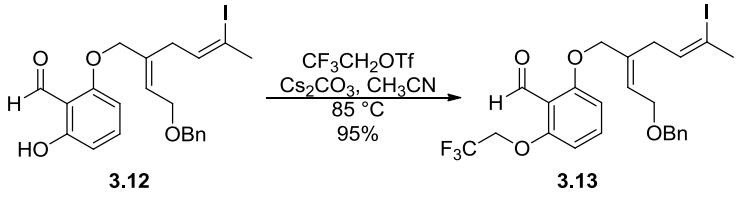
azodicarboxylate (3.45 mL, 17.8 mmol) at 0 °C over 30 min. After the addition was completed, stirring continued for 1.0 h at 0 °C, and then the reaction was warmed to r.t. and stirred overnight. The reaction was concentrated and the residue was taken up in ethyl acetate. The solid was filtered off and the filtrate was concentrated again. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to provide a colorless oil (7.38 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 8.4 Hz, 1H), 7.37 – 7.25 (m, 5H), 6.59 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.55 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.02 (tt, *J* = 6.5, 1.2 Hz, 1H), 5.62 (tq, *J* = 7.1, 1.4 Hz, 1H), 4.56 (d, *J* = 1.2 Hz, 2H), 4.54 (s, 2H), 4.20 (d, *J* = 6.5 Hz, 2H), 3.02 (d, *J* = 7.1 Hz, 2H), 2.48 (q, *J* = 1.4 Hz, 3H), 1.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.43, 157.96, 157.94, 138.34, 136.40, 135.31, 132.65, 128.55 (2C), 128.04 (2C), 127.78, 126.85, 109.54, 106.71, 105.35, 103.73, 102.40, 72.64, 72.59, 66.47, 36.82, 33.67, 25.80 (2C); IR (film) 2995, 2941, 2912, 2854, 1737, 1606, 1583, 1481, 1454, 1377, 1330, 1259, 1205, 1080, 921, 802, 738, 690 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{25}H_{27}INaO_5$ $[M+Na]^+$: 557.0795, found: 557.0791.



3.11 **3.12**

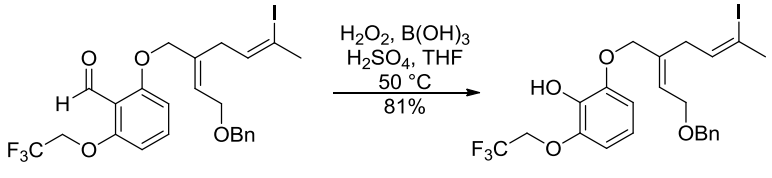
To a solution of acetonide (13.2 g, 24.7 mmol) in CH_2Cl_2 (170 mL) cooled at -78 °C, DIBAL/CH_2Cl_2 (1.0M, 74.2 mL) was added dropwise. The reaction solution was stirred at -78 °C for 3 h and then quenched by ethyl acetate (25 mL) and saturated Rochelle's salt solution (150 mL). After more ethyl acetate (300 mL) was added, the

mixture was warmed to r.t. and stirred overnight. Two clear layers formed and the upper organic layer was decanted and the rest aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with water (3 × 150 mL) and brine (150 mL) and dried over anhydrous Na_2SO_4. Filtration and removal of solvent provided a light yellow oil (11.6 g, 98% yield). This crude product was used without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 10.39 (s, 1H), 7.41 – 7.25 (m, 5H), 7.37 (t, *J* = 8.4 Hz, 1H), 6.52 (dt, *J* = 8.5, 0.7 Hz, 1H), 6.34 (dd, *J* = 8.3, 0.7 Hz, 1H), 5.86 (tt, *J* = 6.4, 1.2 Hz, 1H), 5.35 (tq, *J* = 6.8, 1.4 Hz, 1H), 4.54 (s, 2H), 4.51 (q, *J* = 1.0 Hz, 2H), 4.16 (d, *J* = 6.4 Hz, 2H), 2.99 (d, *J* = 6.8 Hz, 2H), 2.47 (q, *J* = 1.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.36, 163.77, 161.45, 138.40, 138.04, 135.37, 131.86, 128.56 (2C), 127.96 (2C), 127.88, 127.14, 111.08, 110.15, 103.04, 102.11, 72.79, 71.85, 66.16, 36.58, 33.61; IR (film) 3219, 3061, 3028, 2883, 2856, 2791, 1643, 1494, 1462, 1334, 1311, 1238, 1170, 1091, 1028, 837, 783, 719, 499 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{22}H_{24}IO_4$ $[M+H]^+$: 479.0714, found: 479.0722.



In a high-pressure flask was charged phenol (12.8 g, 26.8 mmol), cesium carbonate (8.73 g, 26.8 mmol), 2, 2, 2-trifluoroethyl trifluoromethanesulfonate (5.80 mL, 40.2 mmol) and dry acetonitrile (250 mL). The flask was flushed with N_2 for 5 min., capped and heated to 85 °C (bath temperature). The reaction mixture was stirred

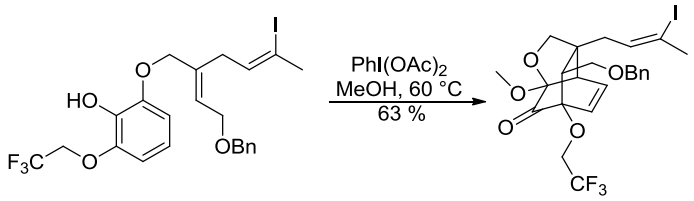
at 85 °C for 3.0 h and the solution gradually turned from light yellow to colorless. After cooling to r.t., the reaction mixture was partitioned between ethyl acetate (300 mL) and water (200 mL). The organic phase was separated and the aqueous phase was washed with saturated $NaHCO_3$ (3 × 100 mL). The aqueous phase was back-extracted with ethyl acetate (100 mL). The combined organic phases were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to afford a light yellow oil (14.3 g, 95% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.54 (s, 1H), 7.43 (t, *J* = 8.5 Hz, 1H), 7.37 – 7.26 (m, 5H), 6.68 (d, *J* = 8.5 Hz, 1H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.92 (tt, *J* = 6.5, 1.1 Hz, 1H), 5.45 (tq, *J* = 6.8, 1.4 Hz, 1H), 4.53 (s, 2H), 4.53 (s, 2H), 4.41 (q, *J* = 8.1 Hz, 2H), 4.17 (d, *J* = 6.5 Hz, 2H), 2.99 (d, *J* = 6.8 Hz, 2H), 2.48 (q, *J* = 1.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.31, 161.12, 159.58, 138.17, 135.66, 135.31, 132.15, 128.54 (2C), 127.99 (2C), 127.83, 126.95, 123.24 (q, *J* = 278.4 Hz), 116.01, 107.54, 106.97, 102.77, 72.69, 72.29, 67.34 (q, *J* = 35.9 Hz), 66.28, 36.61, 33.60; IR (film) 2860, 2775, 1689, 1597, 1473, 1454, 1284, 1246, 1165, 1122, 1028, 975, 825, 777, 738, 698, 667 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{24}H_{25}F_3IO_4$ $[M+H]^+$: 561.0744, found: 561.0737.



3.13 **3.14**

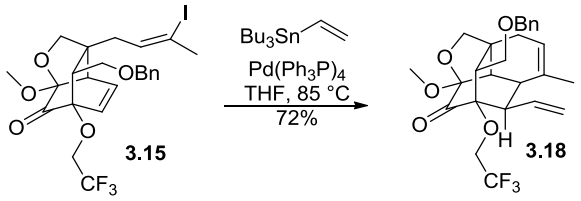
In a high-pressure flask, 10 M sulfuric acid (7.6 mL, 76.0 mmol) was added to a suspension of boric acid (2.36 g, 38.2 mmol) in THF (60 mL) with stirring. Heat was

generated during addition. After the flask was cooled to r.t. in air, hydrogen peroxide (30 wt% in water, 1.30 mL, 11.5 mmol) was added slowly. After stirring at r.t. for 1.0 h, aldehyde (4.28 g, 7.64 mmol) in THF (16 mL) was added. The high-pressure flask was then capped and immersed in 50 °C oil bath and heated for 4.0 h. The reaction was cooled to r.t., diluted with ethyl acetate (100 mL), and washed with water (3 × 50 mL) and brine (2 × 50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (10% ethyl acetate/hexanes) to yield a light yellow oil (3.40 g, 81%). 1H NMR (400 MHz, CDCl3) δ 7.39 – 7.25 (m, 5H), 6.74 (t, J = 8.3 Hz, 1H), 6.63 (td, J = 8.1, 1.4 Hz, 2H), 5.84 (tt, J = 6.4, 1.1 Hz, 1H), 5.57 (s, 1H), 5.37 (tq, J = 6.8, 1.5 Hz, 1H), 4.52 (s, 2H), 4.51 (s, 2H), 4.42 (q, J = 8.3 Hz, 2H), 4.15 (d, J = 6.4 Hz, 2H), 2.98 (d, J = 6.8 Hz, 2H), 2.47 (q, J = 1.5 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 146.81, 145.33, 138.11, 136.81, 135.80, 132.08, 128.55 (2C), 127.98 (2C), 127.87, 127.19, 123.56 (q, J = 278.6 Hz), 119.23, 110.22, 108.39, 102.87, 72.77, 72.68, 67.86 (q, J = 35.3 Hz), 66.22, 36.62, 33.60; IR (film) 3520, 3030, 2947, 2916, 2858, 1610, 1504, 1479, 1454, 1359, 1280, 1211, 1165, 1112, 1087, 968, 736, 698 cm^{-1}; HRMS (ESI) m/z calcd. for C23H24F3INaO4 [M+Na]+: 571.0564, found: 571.0562.



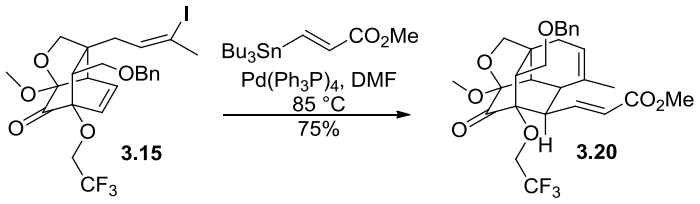
3.14 **3.15**

To a 500-mL 3-necked round-bottom flask equipped with a reflux condenser was charged a solution of iodobenzene diacetate (3.03 g, 9.41 mmol) in methanol (290 mL). The solution was heated to 60 °C and a solution of s.m. (1.72 g, 3.14 mmol) in methanol (24 mL) was added over 2.5 h via syringe pump. Upon the completion of addition, the reaction was stirred at 60 °C for 2 h then cooled to r.t. and concentrated. The crude product was purified by column chromatography (15% ethyl acetate/hexanes) to provide a light yellow oil (1.14g, 63% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.22 (m, 5H), 6.24 – 6.10 (m, 2H), 5.48 (ddq, *J* = 7.9, 6.5, 1.4 Hz, 1H), 4.44 (s, 2H), 4.32 – 4.11 (m, 2H), 4.01 (d, *J* = 8.2 Hz, 1H), 3.82 (d, *J* = 8.2 Hz, 1H), 3.76 (dd, *J* = 10.3, 2.4 Hz, 1H), 3.53 (s, 3H), 3.52 – 3.43 (m, 1H), 3.07 (dd, *J* = 6.6, 1.9 Hz, 1H), 2.68 (ddq, *J* = 15.2, 6.5, 1.4 Hz, 1H), 2.54 (m, 1H), 2.53 (q, *J* = 1.4 Hz, 3H), 2.37 (ddd, *J* = 15.2, 7.7, 1.2 Hz, 1H); ^{13}C NMR (101 MHz, Chloroform-d) δ 198.39, 137.82, 130.22, 129.67, 128.63, 128.50 (2C), 127.96 (2C), 127.87, 123.65 (q, *J* = 277.8 Hz), 105.74, 99.49, 85.17, 78.72, 73.54, 66.45, 64.03 (q, *J* = 35.1 Hz), 52.16, 50.31, 49.17, 47.24, 37.80, 34.06; IR (film) 2949, 2914, 2887, 1755, 1365, 1282, 1205, 1161, 1118, 1091, 1028, 985, 966, 889, 736, 698 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{24}H_{27}F_3IO_5$ $[M+H]^+$: 579.0849, found: 579.0843.



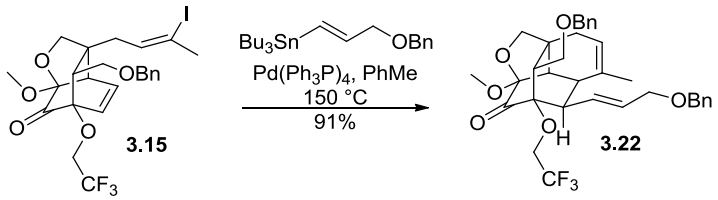
In a 4-mL clear vial was charged a solution of vinyl iodide (5.0 mg, 0.00865 mmol) in THF (0.5 mL). After flushing the solution with N_2 for 10 min, tetrakis(triphenylphosphine)palladium(0) (10 mg, 0.00865 mmol) was added. The vial was capped and heated at 85 °C for 1 h. After which, the reaction was cooled to r.t. and tributyl(vinyl)tin (0.0051 mL, 0.0173 mmol) was added under N_2. The reaction was heated again at 85 °C for 16 h, then cooled to r.t. and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to provide a colorless oil (3.0 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.25 (m, 5H), 5.54 (ddq, *J* = 3.8, 2.6, 1.3 Hz, 1H), 5.34 (dt, *J* = 16.1, 10.0 Hz, 1H), 5.18 – 5.15 (m, 1H), 5.15 – 5.10 (m, 1H), 4.51 – 4.41 (m, 2H), 4.19 (dq, *J* = 10.8, 8.6 Hz, 1H), 3.96 (dq, *J* = 10.8, 8.6 Hz, 1H), 3.89 (d, *J* = 7.3 Hz, 1H), 3.78 (d, *J* = 7.3 Hz, 1H), 3.67 (dd, *J* = 9.5, 1.8 Hz, 1H), 3.58 (s, 3H), 3.60 – 3.52 (m, 1H), 2.79 (m, 1H), 2.71 – 2.66 (m, 1H), 2.62 (ddq, *J* = 18.4, 4.7, 1.7 Hz, 1H), 2.46 (dt, *J* = 9.9, 1.7 Hz, 1H), 2.23 (d, *J* = 3.8 Hz, 1H), 2.07 (dtd, *J* = 18.2, 2.6, 1.5 Hz, 1H), 1.71 (dt, *J* = 2.8, 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 203.20, 137.97, 134.90, 133.60, 128.53 (2C), 127.92, 127.90 (2C), 123.73 , 123.72 (q, *J* = 277.8 Hz), 120.94, 103.37, 81.99, 78.84, 73.15, 68.19, 61.85 (q, *J* = 35.0 Hz), 52.09, 46.43, 45.43, 43.73, 42.13, 35.30, 29.83, 25.25; IR (film) 2948, 2923, 2890, 1748, 1454, 1284, 1219, 1161, 1101, 1076, 993, 922, 888,

736, 696 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{26}H_{30}F_3O_5$ $[M+H]^+$: 479.2039, found: 479.2037.



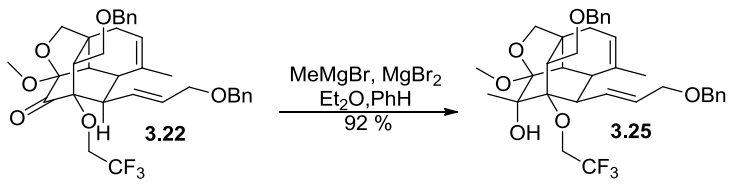
In a high-pressure tube was charged a solution of vinyl iodide (25.0 mg, 0.0432 mmol) in DMF (2.2 mL). After flushing the solution with N_2 for 10 min, tetrakis(triphenylphosphine)palladium(0) (0.5 mg, 0.000432 mmol) and (*E*)-methyl 3-(tributylstannyl)acrylate (32 mg, 0.864 mmol) were added successively. The tube was flushed with N_2 for 10 min again, capped and heated at 85 °C for 18 h. After cooling to r.t. the reaction mixture was poured onto water (10 mL) and extracted with ethyl acetate (3 × 5 mL). The combined extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to provide a light yellow solid, which was further purified by trituration with methanol. The resultant white solid was collected by vacuum filtration (17.3 mg, 75% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 6.43 (dd, *J* = 15.2, 10.6 Hz, 1H), 5.88 (dd, *J* = 15.2, 0.7 Hz, 1H), 5.58 (tt, *J* = 2.8, 1.4 Hz, 1H), 4.47 (s, 2H), 4.19 (dq, *J* = 10.9, 8.5 Hz, 1H), 3.91 (d, *J* = 7.3 Hz, 1H), 3.81 (d, *J* = 7.3 Hz, 1H), 3.75 (dq, *J* = 10.9, 8.5 Hz, 1H), 3.75 (s, 3H), 3.64 – 3.52 (m, 2H), 3.60 (s, 3H), 2.95 – 2.84 (m, 1H), 2.74 – 2.67 (m, 1H), 2.62 (ddd, *J* = 18.4, 4.4, 1.7 Hz, 1H), 2.50 – 2.44 (m, 1H), 2.27 (d, *J* = 3.8 Hz, 1H), 2.09 (dq, *J* = 18.3, 2.3 Hz, 1H), 1.65 (dt, *J* = 2.8, 1.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

202.29, 166.21, 143.43, 137.70, 134.07, 128.57 (2C), 128.14 (2C), 128.04, 126.13, 124.70, 123.49 (q, J = 277.7 Hz), 103.24, 81.99, 79.17, 73.36, 67.72, 61.94 (q, J = 35.4 Hz), 52.33, 51.77, 45.75, 44.93, 42.88, 42.24, 35.09, 29.76, 24.79; IR (film) 2950, 2890, 1761, 1722, 1653, 1436, 1283, 1240, 1163, 1092, 991, 733, 700 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{28}H_{31}F_3NaO_7$ $[M+Na]^+$: 559.1914, found: 559.1914.



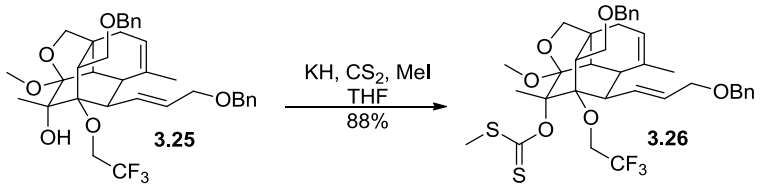
In a 15-mL high-pressure tube was charged a solution of vinyl iodide (400.0 mg, 0.692 mmol) in toluene (7.0 mL). After flushing the solution with N_2 for 15 min., tetrakis(triphenylphosphine)palladium(0) (40.0 mg, 0.0346 mmol) and (*E*)-(3-(benzyloxy)prop-1-en-1-yl)tributylstannane (0.4 mL, 0.900 mmol) were added successively. The tube was flushed with N_2 for 10 min. again, capped and heated at 150 °C for 18 h. The reaction solution turned from yellow to olive over time and in some occasions a black precipitate formed on the glass wall. After cooling to r.t. the reaction mixture was filtered through a Celite pad and the filtrate was concentrated and purified by column chromatography (10% ethyl acetate/hexanes) to provide a light yellow oil (375.2 mg, 91% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.20 (m, 10H), 5.68 (dt, J = 15.2, 5.5 Hz, 1H), 5.54 (dt, J = 4.0, 2.2 Hz, 1H), 5.24 (ddt, J = 15.2, 10.2, 1.5 Hz, 1H), 4.48 (d, J = 4.0 Hz, 2H), 4.41 (d, J = 1.4 Hz, 2H), 4.24 (dq, J = 11.0, 8.6 Hz, 1H), 4.00 (ddd, J = 5.5, 2.3, 1.5 Hz, 2H), 3.95 – 3.85 (m, 2H), 3.79 (d, J = 7.3 Hz, 1H), 3.63 (dd, J = 9.4, 1.7 Hz, 1H), 3.59 (s, 3H), 3.54 (dd, J = 9.7, 9.4 Hz,

1H), 2.84 (dd, *J* = 10.7, 10.2 Hz, 1H), 2.68 (dd, *J* = 10.7, 3.8 Hz, 1H), 2.61 (ddd, *J* = 18.4, 4.4, 2.1 Hz, 1H), 2.47 (dt, *J* = 9.7, 1.7 Hz, 1H), 2.25 (d, *J* = 3.8 Hz, 1H), 2.08 (d, *J* = 18.4 Hz, 1H), 1.70 (dt, *J* = 2.7, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.08, 138.67, 137.89, 134.94, 133.00, 128.55 (2C), 128.50 (2C), 127.98, 127.94 (2C), 127.87, 127.64, 127.58 (2C), 123.83, 123.77 (q, *J* = 277.6 Hz), 103.41, 82.03, 79.11, 73.18, 71.60, 69.86, 68.13, 61.90 (q, *J* = 35.1 Hz), 52.17, 45.51, 45.34, 43.33, 42.18, 35.30, 29.83, 25.25; IR (film) 2943, 2887, 2850, 1751, 1452, 1282, 1161, 1070, 991, 887, 736, 698 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{34}H_{37}F_3NaO_6$ $[M+Na]^+$: 621.2434, found: 621.2439.



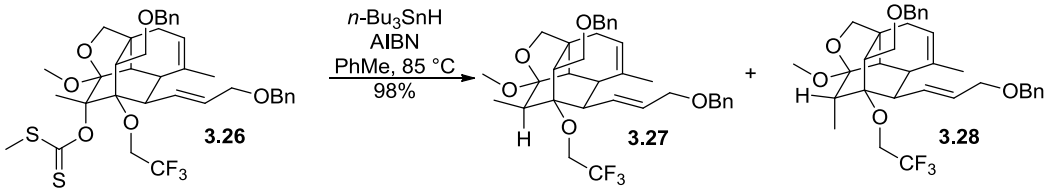
Magnesium bromide diethyl etherate (542.0 mg, 2.10 mmol) in a flask was dried by heating gently under vacuum. After the flask was cooled to r.t., ketone (837.6 mg, 1.40 mmol) in anhydrous ethyl ether (12.0 mL) was added, followed by anhydrous benzene (2.5 mL). The mixture turned into a clear solution. (Note: When $MgBr_2$ dissolves in diethyl ether it forms two layers of liquid. The button layer contains $MgBr_2$ at 39 wt% and the top layer 3 wt%. Addition of benzene can increase the solubility and make a clear solution. This operation does not seem to affect the yield or stereoselectivity of the reaction and therefore could be omitted.) The solution was cooled to 0 °C with vigorous stirring. Grignard reagent (3.0 M, 0.70 mL, 2.10 mmol) was added dropwise while the reaction solution turned form colorless to light

yellow. After the addition was completed, the reaction mixture was warmed to r.t. and stirred for 1.0 h, then quenched by saturated NH_4Cl solution at 0 °C and diluted with water and ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash column (10-15% ethyl acetate/hexanes) to afford a colorless oil (790.2 mg, 92% yield), which solidified under high vacuum. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.19 (m, 10H), 5.74 (dt, *J* = 15.3, 5.6 Hz, 1H), 5.53 – 5.39 (m, 2H), 4.48 (s, 2H), 4.47 (d, *J* = 11.9 Hz, 1H), 4.39 (d, *J* = 11.9 Hz, 1H), 4.23 (dq, *J* = 11.3, 8.5 Hz, 1H), 4.02 (dq, *J* = 11.3, 8.5 Hz, 1H), 3.99 (dd, *J* = 5.6, 1.4 Hz, 2H), 3.95 (dd, *J* = 8.9, 1.9 Hz, 1H), 3.80 (td, *J* = 11.3, 2.0 Hz, 1H), 3.71 (d, *J* = 6.8 Hz, 1H), 3.55 (m, 1H), 3.53 (d, *J* = 6.8 Hz, 1H), 3.35 (s, 3H), 3.35 (s, 1H), 2.51 (dd, J = 11.3, 3.5 Hz, 1H), 2.47 (m, 1H), 2.19 (dt, *J* = 10.3, 2.0 Hz, 1H), 1.96 (dtd, *J* = 18.6, 2.7, 1.2 Hz, 1H), 1.89 (d, *J* = 3.5 Hz, 1H), 1.65 (dt, *J* = 2.9, 1.6 Hz, 3H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.71, 138.53, 135.69, 131.88, 131.47, 128.48 (2C), 128.43 (2C), 127.71 (2C), 127.62, 127.60, 127.51 (2C), 124.27 (q, *J* = 277.7 Hz), 122.45, 107.10, 81.38, 79.56, 79.49, 72.69, 71.85, 70.40, 69.10, 61.96 (q, *J* = 34.0 Hz), 49.99, 47.83, 40.78, 39.98, 35.43, 35.10, 29.62, 25.59, 17.48; IR (film) 3535, 2939, 2858, 1452, 1282, 1163, 1118, 1095, 1016, 960, 856, 734, 696 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{35}H_{42}F_3O_6$ $[M+H]^+$: 615.2928, found: 615.2926.



Potassium hydride (30 wt% in mineral oil, 0.98 g, 7.34 mmol) was washed with dry pentane under N_2 for three times, suspended in THF (15 mL) and cooled to 0 °C. Alcohl (1.13 g, 1.83 mmol) in THF (3.3 mL) was added dropwise. After the reaction was stirred at 0 °C for 2.0 h, freshly distilled carbon disulfide (1.11 mL, 18.3 mmol) was added dropwise. The reaction was stirred at 0 °C for 30 min. and r.t. 4.0h. After that period of time, the reaction was cooled to 0 °C again and methyl iodide (1.14 mL, 18.3 mmol) was added dropwise. The resultant mixture was allowed to warm up to r.t. and stirred for 20 h. The reaction was quenched by water at 0 °C and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was triturated with hexane and an off-white solid was collected by vacuum filtration. The filtrate was concentrated and purified by flash column chromatography (15% ethyl acetate/hexanes) to afford another crop of white solid. All solids were combined and weighed 1.13g (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.20 (m, 10H), 5.82 (dt, J = 15.2, 5.5 Hz, 1H), 5.53 – 5.37 (m, 2H), 4.51 (s, 2H), 4.44 (q, J = 11.8 Hz, 2H), 4.12 – 3.96 (m, 3H), 3.94 – 3.77 (m, 3H), 3.73 (d, J = 7.0 Hz, 1H), 3.62 – 3.54 (m, 1H), 3.54 (d, J = 7.2 Hz, 1H), 3.24 (s, 3H), 2.65 (d, J = 11.8, 3.5 Hz, 1H), 2.54 (s, 3H), 2.52 – 2.41 (m, 1H), 2.20 (dt, J = 10.3, 2.0 Hz, 1H), 2.03 (s, 3H), 2.01 – 1.93 (m,

1H), 1.95 (d, *J* = 3.5 Hz, 1H), 1.69 (dt, *J* = 2.8, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.63, 138.60, 138.35, 135.55, 132.83, 130.06, 128.51 (2C), 128.47 (2C), 127.72 (2C), 127.70, 127.67, 127.50 (2C), 123.84 (q, *J* = 277.8 Hz), 122.67, 107.94, 97.60, 81.57, 80.64, 72.79, 72.24, 70.33, 69.04, 61,90 (q, *J* = 34.3 Hz), 49.18, 47.30, 40.95, 40.48, 35.81, 34.94, 29.52, 25.57, 20.08, 15.50; IR (film) 2935, 2860, 1282, 1222, 1163, 1109, 1016, 962, 734, 696 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{37}H_{44}F_3O_6S_2$ $[M+H]^+$: 705.2526, found: 705.2521.

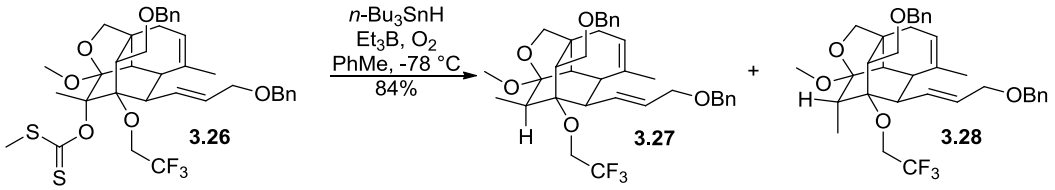


A mixture of xanthate (45.0 mg, 0.0638 mmol), tributyltin hydride (0.085 mL, 0.319 mmol) and azobisisobutyronitrile (5.4 mg, 0.0319 mmol) in toluene (1.3 mL) was heated at 85 °C for 1 h, then cooled to r.t. and concentrated. The crude product was purified by column chromatography (10-15% ethyl acetate/hexanes) to afford product **3.27** (lower R_f, white solid, 31.2 mg, 82% yield) and **3.28** (higher R_f, white solid, 6.0 mg, 16% yield).

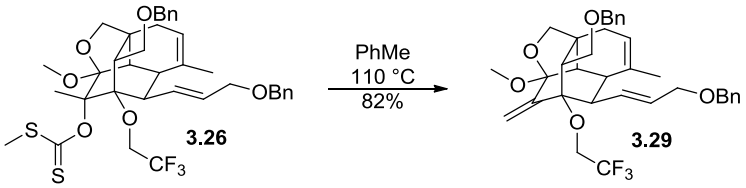
Compound **3.27**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.19 (m, 10H), 5.68 (dt, *J* = 15.3, 5.6 Hz, 1H), 5.50 – 5.36 (m, 2H), 4.49 (s, 2H), 4.48 (d, *J* = 11.8 Hz, 1H), 4.40 (d, *J* = 11.8 Hz, 1H), 4.07 – 3.89 (m, 3H), 3.87 (dd, *J* = 9.0, 1.9 Hz, 1H), 3.73 (d, *J* = 7.0 Hz, 1H), 3.67 (dq, *J* = 10.2, 8.1 Hz, 1H), 3.58 (d, *J* = 7.0 Hz, 1H), 3.52 (dd, *J* = 10.4, 9.0 Hz, 1H), 3.31 (s, 3H), 2.68 (td, *J* = 11.0, 1.8 Hz, 1H), 2.58 (dd, *J* = 11.3, 3.6 Hz, 1H), 2.52 (ddd, *J* = 18.4, 4.3, 2.0 Hz, 1H), 2.21 (dt, *J* = 10.4, 1.9 Hz, 1H), 2.02 (q,

J = 6.8 Hz, 1H), 1.96 (m, 2H), 1.65 (dt, *J* = 2.9, 1.6 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.57, 138.53, 134.70, 131.64, 131.32, 128.53 (2C), 128.45 (2C), 127.77 (2C), 127.69, 127.65, 127.56 (2C), 123.53, 124.05 (q, *J* = 277.1 Hz), 109.63, 81.53, 77.20, 72.78, 71.98, 70.25, 68.64, 59.93 (q, *J* = 34.5 Hz), 49.62, 48.81, 47.52, 46.32, 40.87, 40.49, 35.66, 30.24, 25.60, 7.69; IR (film) 2923, 2855, 1454, 1281, 1161, 1114, 1013, 966, 926, 735, 696 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{35}H_{42}F_3O_5$ $[M+H]^+$: 599.2978, found: 599.2980.

Compound **3.28**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 – 7.20 (m, 10H), 5.62 (dt, *J* = 15.1, 5.9 Hz, 1H), 5.44 (dt, *J* = 4.3, 2.0 Hz, 1H), 5.27 (dd, *J* = 15.1, 10.1 Hz, 1H), 4.49 (d, *J* = 12.2 Hz, 1H), 4.43 (d, *J* = 12.3 Hz, 2H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.02 (ddd, *J* = 12.8, 5.8, 1.4 Hz, 1H), 3.96 (ddd, *J* = 12.8, 5.8, 1.4 Hz, 1H), 3.77 (d, *J* = 6.9 Hz, 1H), 3.66 – 3.52 (m, 3H), 3.50 (dd, *J* = 9.6, 1.6 Hz, 1H), 3.36 (t, *J* = 9.8 Hz, 1H), 3.32 (s, 3H), 2.72 (t, *J* = 10.6 Hz, 1H), 2.46 – 2.39 (m, 2H), 2.24 (q, *J* = 7.1 Hz, 1H), 2.12 (d, *J* = 10.0 Hz, 1H), 2.01 (d, *J* = 18.2 Hz, 1H), 1.89 (d, *J* = 3.6 Hz, 1H), 1.66 (s, 3H), 0.96 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, extracted for HSQC and MHBC) 128.5 (2C), 127.86(2C), 127.77(3C), 127.5 (3C), 138.94, 138.07, 136.05, 131.73, 130.47, 124.03, 122.26, 108.77, 81.06, 77.01, 73.11, 71.08, 70.42, 68.32, 59.23, 49.87, 47.97, 47.66, 40.14, 39.00, 38.97, 34.78, 29.77, 25.26, 9.07; IR (film) 2923, 2853, 1454, 1368, 1279, 1161, 1114, 1016, 968, 916, 735, 698 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{35}H_{42}F_3O_5$ $[M+H]^+$: 599.2978, found: 599.2978.

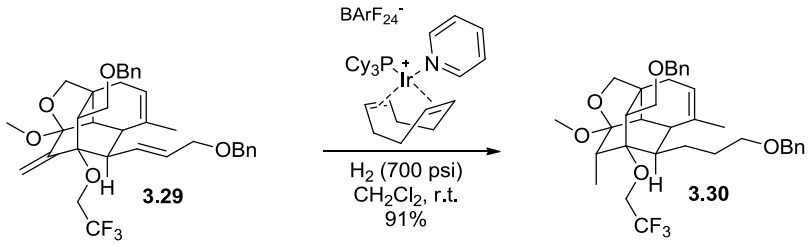


A mixture of xanthate (10.0 mg, 0.0142 mmol), tributyltin hydride (0.009 mL, 0.0355 mmol) and triethylborane (1.0 M in THF, 0.01 mL) in toluene (1.4 mL) was cooled to -78 °C and O_2 was bubbled through for 5 min. The reaction was stirred at -78 °C for 1.0 h under O_2 atmosphere, then warmed to r.t. and concentrated. Crude ^{1}H-NMR showed the ratio of **3.27** to **3.28** is about 17:1. The major product **3.27** was isolated by column chromatography (10% ethyl acetate/hexanes) as a white solid (14.3 mg, 84% yield).



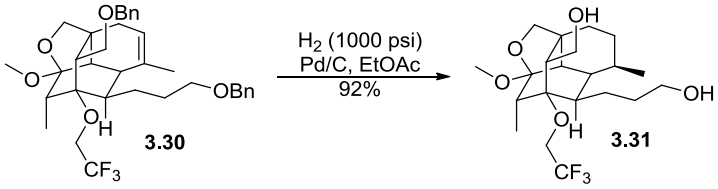
A solution of xanthate (3.02 g, 4.28 mmol) in toluene (43.0 mL) was heated at 110 °C for 4 h. After cooling to r.t. the reaction mixture was concentrated. The residue was triturated with 5% ethyl acetate/hexanes. A white solid was collected by vacuum filtration. The filtrate was concentrated and purified by flash column (10-15% ethyl acetate/hexanes) to afford another crop of white solid. The solids are combined and weighed 2.09 g (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.22 (m, 10H), 5.63 (dtd, J = 15.1, 5.8, 0.6 Hz, 1H), 5.47 (m, 1H), 5.46 (d, J = 0.7 Hz, 1H), 5.25 (ddt, J = 15.1, 10.3, 1.5 Hz, 1H), 5.05 (s, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 11.8 Hz,

1H), 4.44 (d, J = 12.1 Hz, 1H), 4.36 (d, J = 11.8 Hz, 1H), 4.05 – 3.93 (m, 3H), 3.80 (d, J = 7.0 Hz, 1H), 3.64 (d, J = 7.1 Hz, 1H), 3.56 – 3.37 (m, 3H), 3.40 (s, 3H), 2.71 – 2.62 (m, 1H), 2.60 – 2.54 (m, 1H), 2.50 – 2.41 (m, 1H), 2.24 (dt, J = 9.4, 1.9 Hz, 1H), 2.16 (d, J = 3.5 Hz, 1H), 2.05 (dtd, J = 18.2, 2.5, 1.2 Hz, 1H), 1.67 (dt, J = 2.8, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.30, 138.85, 137.87, 136.06, 132.23, 129.82, 128.52 (2C), 128.42 (2C), 127.97, 127.92 (2C), 127.61 (2C), 127.53, 124.07 (q, J = 277.8 Hz), 122.78, 105.96, 104.75, 81.33, 77.79, 73.14, 71.23, 70.26, 67.85, 60.17 (q, J = 34.4 Hz), 50.60, 49.78, 45.37, 41.62, 41.41, 35.60, 30.00, 25.31; IR (film) 2931, 2852, 1452, 1367, 1282, 1166, 1103, 1010, 923, 854, 734, 696 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{35}H_{40}F_3O_5$ $[M+H]^+$: 597.2822, found: 597.2828.



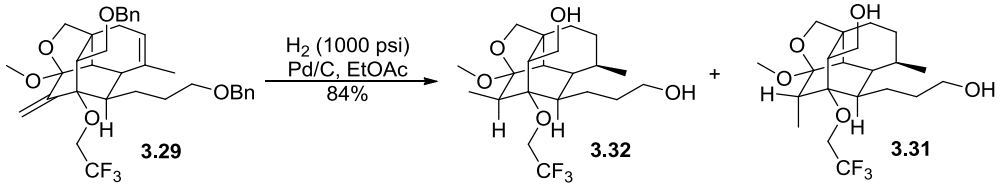
In a 4-mL clear glass vial, triene (124.7 mg, 0.209 mmol) was dissolved in CH_2Cl_2 (1.0 mL), and iridium catalyst[3] (8.0 mg, 0.00522 mmol, 0.025 eq.) was added. The resultant red solution was bubbled with H_2 for 1.0 min. and the color was discharged immediately. Six of this vial was placed in a hydrogenation bomb and stirred at r.t. under 700 psi of H_2 for 16 h. The combined reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford a white solid (688.6 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 10H), 5.50 – 5.42 (m, 1H), 4.50

(d, J = 11.9 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.46 (d, J = 11.9 Hz, 1H), 4.40 (d, J = 11.8 Hz, 1H), 3.74 (d, J = 7.0 Hz, 1H), 3.64 – 3.54 (m, 2H), 3.54 – 3.50 (m, 1H), 3.52 (d, J = 7.0 Hz, 1H), 3.46 (ddd, J = 9.5, 7.8, 5.5 Hz, 1H), 3.38 (dt, J = 9.6, 7.1 Hz, 1H), 3.30 (s, 3H), 3.28 (t, J = 10.0 Hz, 1H), 2.53 – 2.45 (m, 2H), 2.19 (q, J = 7.1 Hz, 1H), 2.07 (dt, J = 10.6, 1.9 Hz, 1H), 2.00 – 1.89 (m, 2H), 1.88 (d, J = 3.6 Hz, 1H), 1.78 – 1.68 (m, 1H), 1.74 (s, 3H), 1.63 – 1.54 (m, 1H), 1.47 (dtd, J = 14.0, 8.2, 2.5 Hz, 1H), 1.11 (dtd, J = 13.0, 7.8, 4.9 Hz, 1H), 0.89 (d, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.81, 138.25, 136.23 , 128.43 (2C), 128.4 (q, J = 278.1 Hz), 128.34 (2C), 127.73, 127.69 (2C), 127.64 (2C), 127.45, 123.19, 108.65, 81.09, 77.91, 73.00, 72.82, 70.48, 68.18, 59.06 (q, J = 34.5 Hz), 49.85, 48.01, 47.82, 40.53, 40.43, 35.51, 34.38, 31.85, 29.87, 25.48, 21.10, 8.82; IR (film) 3028, 2929, 2856, 1496, 1454, 1365, 1280, 1201, 1163, 1112, 966, 916, 734, 696 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{35}H_{44}F_3O_5$ $[M+H]^+$: 601.3135, found: 601.3132.



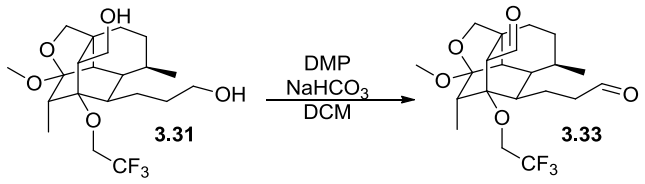
In a 2-mL clear glass vial, palladium on carbon (10 wt%, 35.0 mg, 0.0328 mmol) was added to a solution of alkene (19.7 mg, 0.0328 mmol) in ethyl acetate (0.82 mL). Seven of this reaction vial were placed in a hydrogenation bomb and stirred at r.t. under 1000 psi H_2 for 22 h. The reaction mixtures were filtered through a Celite pad and the filtrates were combined and triturated with 30% ethyl acetate/hexanes. A white solid was collected by vacuum filtration and the filtrate was

concentrated and purified by column chromatography (50% ethyl acetate/hexanes) to afford another crop of white solid. The solids were combined and weighed 89.3 mg (92% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 3.99 – 3.71 (m, 4H), 3.60 – 3.49 (m, 1H), 3.57 (d, *J* = 6.5 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.37 (d, *J* = 6.5 Hz, 1H), 3.28 (s, 3H), 2.31 – 2.24 (m, 1H), 2.22 – 2.16 (m, 1H), 2.14 (q, *J* = 7.1 Hz, 1H), 2.03 (dt, *J* = 10.6, 2.5 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.77 – 1.56 (m, 5H), 1.59 (d, *J* = 2.5 Hz, 1H), 1.54 – 1.36 (m, 3H), 1.22 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.28 (q, *J* = 277.6 Hz), 108.35, 81.35, 80.88, 62.20, 59.78 (q, *J* = 34.3 Hz), 59.15, 49.97, 49.35, 47.17, 47.15, 41.65, 38.23, 35.42, 34.50, 33.21, 28.81, 27.91, 21.24, 18.89, 9.07; IR (film) 3373, 2941, 2875, 2499, 1390, 1282, 1159, 1122, 1045, 983, 970 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{34}F_3O_5$ $[M+H]^+$: 423.2353, found: 423.2346.

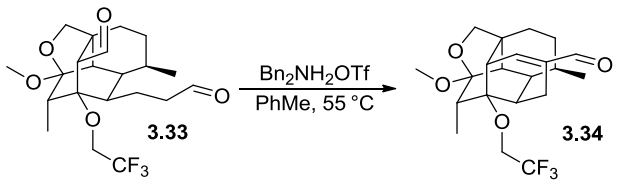


In a 2-mL clear glass vial, palladium on carbon (10 wt%, 17.8 mg, 0.0168 mmol) was added to a solution of diene (10.0 mg, 0.0168 mmol) in ethyl acetate (0.60 mL). Five of this vial were placed in a hydrogenation bomb and stirred at r.t. under 1000 psi H_2 for 36 h. The reaction mixtures were filtered through a Celite pad and the filtrates were combined, concentrated and purified by column chromatography (70% ethyl acetate/hexanes) to afford a white solid (6.5:1 inseparable mixture, 29.7 mg, 84% yield). Major diastereomer: ^{1}H NMR (500 MHz, CD_3OD) δ 4.02 (dd, *J* = 11.0,

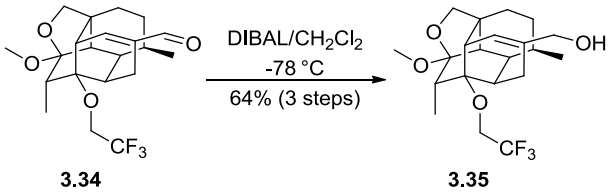
3.6 Hz, 1H), 3.87 – 3.79 (m, 2H), 3.63 (dq, *J* = 11.0, 8.5 Hz, 1H), 3.55 (d, *J* = 6.5 Hz, 1H), 3.51 (t, *J* = 6.4 Hz, 2H), 3.40 (d, *J* = 6.5 Hz, 1H), 3.27 (s, 3H), 2.33 (m, 2H), 2.07 – 2.00 (m, 1H), 1.97 – 1.84 (m, 3H), 1.83 – 1.56 (m, 4H), 1.70 (d, *J* = 2.7 Hz, 1H), 1.53 – 1.34 (m, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.90 (q, *J* = 277.7 Hz), 109.06, 82.95, 81.23, 62.76, 60.30, 60.30 (q, *J* = 34.6 Hz), 49.43, 48.81, 47.22, 47.17, 44.38, 41.96, 38.67, 35.49, 33.13, 29.04, 28.50, 21.63, 20.77, 7.37; IR (film) 3413, 2944, 2917, 2875, 2514, 1458, 1281, 1163, 1118, 1093, 1025, 966 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{34}F_3O_5$ $[M+H]^+$: 423.2353, found: 423.2355.



To a mixture of diol (51.7 mg, 0.122 mmol) and $NaHCO_3$ (51.2 mg, 0.610 mmol) in CH_2Cl_2 (4.8 mL) was added Dess–Martin periodinane (129.8 mg, 0.306 mmol) in one portion at r.t. After stirring for 1.5 h the reaction mixture was filtered through a Celite pad. The filtrate was concentrated, then taken up in diethyl ether (50 mL) and filtered again. The etheral solution was washed with saturated $NaHCO_3$/10% $Na_2S_2O_3$ mixture solution (1:2 v/v, 5 × 6 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product (50.0 mg) was used directly without further purification.

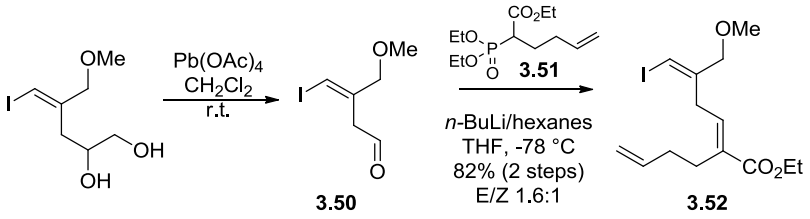


A mixture of dialdehyde (50.0 mg, 0.119 mmol) and dibenzylammonium trifluoroacetate (40.9 mg, 0.131 mmol) in toluene (2.4 mL) was heated at 55 °C for 16 h, while the reaction solution turned to light yellow gradually. After that period of time, the reaction was cooled to r.t. and concentrated. The residue was taken up in diethyl ether and the solid was filtered off. The filtrate was concentrated again, then loaded onto a short silica gel pad and eluted with 30% ethyl acetate/hexanes. The eluate was concentrated to afford a colorless oil (50.9 mg), which was used directly in the next step.



To a solution of aldehyde (50.9 mg, 0.127 mmol) in CH_2Cl_2 (2.3 mL) was added DIBAL (1.0 M in CH_2Cl_2, 0.25 mL) dropwise at -78 °C. The reaction was stirred at -78 °C for 1.5 h then quenched by 10% Rochelle's salt solution (5.0 mL). The mixture was warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (30% ethyl acetate/hexanes) to provide a white solid (31.3

mg, 64% yield over 3 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (dp, *J* = 7.2, 1.5 Hz, 1H), 4.04 (s, 2H), 3.69 – 3.56 (m, 2H), 3.43 – 3.34 (m, 2H), 3.33 (s, 3H), 2.42 (m, 1H), 2.38 – 2.30 (m, 1H), 2.36 (s, 1H), 2.27 (dt, *J* = 11.5, 2.7 Hz, 1H), 2.19 (dd, *J* = 7.2, 3.0 Hz, 1H), 2.12 (q, *J* = 7.2 Hz, 1H), 1.80 – 1.72 (m, 1H), 1.61 (dqd, *J* = 10.4, 7.4, 3.3 Hz, 1H), 1.42 – 1.23 (m, 5H), 1.20 (d, *J* = 7.2 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.08, 124.35 (q, *J* = 278.7 Hz), 116.52, 108.17, 80.55, 79.56, 66.48, 60.31 (q, *J* = 34.3 Hz), 50.18, 47.48, 44.65, 43.04, 41.88, 37.29, 34.86, 29.81, 28.59, 26.86, 25.43, 22.23, 9.17; IR (film) 3427, 2978, 2929, 2891, 1456, 1386, 1280, 1165, 1151, 1120, 968, 864, 732 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}F_3O_4$ $[M+H]^+$: 403.2091, found: 403.2096.



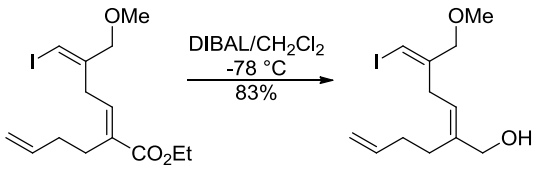
To an ice-water cooled solution of diol (2.03 g, 7.47 mmol) in CH_2Cl_2 (30.0 mL) was added lead (IV) acetate (3.64 g, 8.21 mmol) in portions. After the addition was completed, the reaction mixture was allowed to warm to r.t. and stirred for 1.0 h. The reaction mixture was poured directly over a silica gel pad, filtered and the filter cake was washed with ethyl acetate. The filtrate was concentrated on rotovap and the residue was taken up in ether and filtered through a Celite pad and washed with ethyl ether. The filtrate was concentrated again on rotovap and then placed under high vacuum briefly to remove residual solvents and formaldehyde. The resultant aldehyde crude product was used immediately.

To a solution of phosphonate[4] (11.43 g, 41.1 mmol) in THF (10 mL), *n*-BuLi (2.5 M in hexane, 14.9 mL, 37.4 mmol) was added dropwise at -78 °C with stirring. After 2.0 h, the aforementioned aldehyde in THF (5.0 mL) was added dropwise and the stirring was continued for 6.0 h. The reaction was quenched by saturated NH_4Cl solution (5 mL), warmed to r.t., diluted with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexanes to straight ethyl acetate) to afford the desired product mixture (colorless oil, 2.24 g, E/Z 1.6:1, yield 82%) and recovered phosphonate. The E/Z mixture was further separated by column chromatography (5% ethyl ether/hexanes): high R_f fraction, Z isomer, colorless oil, 0.86 g; low R_f fraction, E isomer, colorless oil, 1.38 g.

Z isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (td, *J* = 1.4, 0.7 Hz, 1H), 5.85 – 5.71 (m, 2H), 5.01 (ddt, *J* = 17.1, 2.0, 1.5 Hz, 1H), 4.96 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.90 (d, *J* = 1.4 Hz, 2H), 3.39 (dq, *J* = 7.5, 0.8 Hz, 2H), 3.31 (s, 3H), 2.37 (ddt, *J* = 8.7, 6.2, 1.0 Hz, 2H), 2.23 – 2.13 (m, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.78, 146.41, 137.81, 136.17, 133.71, 115.29, 79.41, 75.10, 60.48, 58.24, 35.79, 34.12, 33.31, 14.44; IR (film) 2980, 2927, 1708, 1639, 1448, 1377, 1201, 1095, 1026, 912, 785 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{14}H_{21}INaO_3$ $[M+Na]^+$: 387.0428, found: 387.0429.

E isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (tt, *J* = 7.5, 0.6 Hz, 1H), 6.40 (td, *J* = 1.3, 0.6 Hz, 1H), 5.84 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1H), 5.04 (ddt, *J* = 17.1, 2.0, 1.5

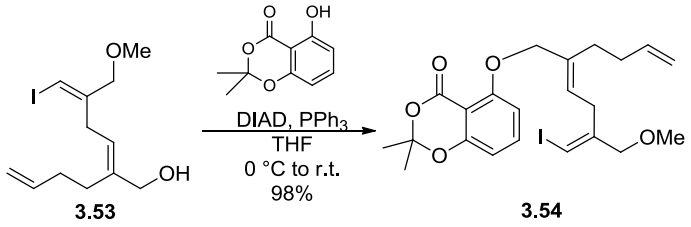
Hz, 1H), 4.97 (ddt, *J* = 10.2, 2.0, 1.1 Hz, 1H), 4.20 (q, *J* = 7.1 Hz, 2H), 3.90 (d, *J* = 1.3 Hz, 2H), 3.31 (s, 3H), 3.14 (dd, *J* = 7.5, 0.6 Hz, 2H), 2.54 – 2.45 (m, 2H), 2.25 – 2.15 (m, 2H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.51, 145.69, 137.97, 137.21, 134.03, 115.25, 80.49, 74.98, 60.66, 58.11, 34.70, 33.37, 26.72, 14.37; IR (film) 2978, 2929, 2819, 1708, 1639, 1448, 1371, 1261, 1199, 1095, 912, 783 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{14}H_{22}IO_3$ $[M+H]^+$: 365.0608, found: 365.0603.



3.52 **3.53**

To a solution of ester (10.1 g, 27.8 mmol) in CH_2Cl_2 (200 mL) was added DIBAL (1.0 M in CH_2Cl_2, 69.5 mL) dropwise at -78 °C. The reaction was stirred at -78 °C for 6.5 h then quenched by 10% Rochelle's salt solution (150 mL), diluted with CH_2Cl_2 (200 mL), warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The combined organic layers were washed with brine (200 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10-25% ethyl acetate/hexanes) to provide a colorless oil (7.54 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, *J* = 1.4, 0.6 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.2, 6.5 Hz, 1H), 5.39 (dddt, *J* = 7.3, 6.7, 1.2, 0.8 Hz, 1H), 5.06 (ddt, *J* = 17.1, 2.0, 1.5 Hz, 1H), 4.98 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H), 4.07 (dq, *J* = 6.1, 1.2 Hz, 2H), 3.89 (d, *J* = 1.4 Hz, 2H), 3.30 (s, 3H), 3.02 (dq, *J* = 7.3, 0.8 Hz, 2H), 2.34 – 2.25 (m, 2H), 2.20 (dddt, *J* = 8.3, 6.5, 5.7, 1.4 Hz, 2H), 1.33 (t, *J* = 6.1 Hz, 1H); ^{13}C

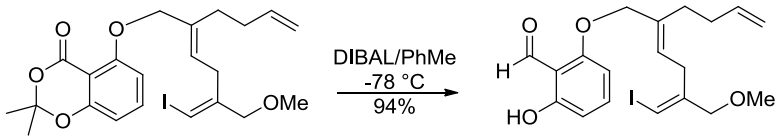
NMR (100 MHz, $CDCl_3$) δ 147.03, 141.10, 138.31, 121.76, 115.11, 79.12, 74.90, 66.85, 58.08, 33.71, 32.70, 27.84; IR (film) 3385, 2926, 2856, 2819, 1639, 1448, 1087, 1064, 912 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{12}H_{19}INaO_2$ $[M+Na]^+$: 345.0322, found: 345.0318.



3.53 **3.54**

To an ice-water cooled solution of alcohol (2.39g, 7.42 mmol), phenol (1.57 g, 8.90 mmol) and triphenylphosphine (2.33 g, 8.90 mmol) in THF (50 mL) was added diisopropyl azodicarboxylate (1.73 mL, 8.90 mmol) slowly. After the addition was completed, stirring continued for 1.0 h at 0 °C and then the reaction mixture was warmed to r.t. naturally and stirred overnight. The reaction was concentrated and the residue was taken up in ethyl acetate. After the solid was filtered off, the filtrate was concentrated again and the residue was purified by column chromatography (20% ethyl acetate/hexanes) to provide a light yellow oil (3.61 g, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (t, *J* = 8.4 Hz, 1H), 6.59 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.54 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.31 – 6.26 (m, 1H), 5.87 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.65 (ddt, *J* = 8.4, 7.3, 1.1 Hz, 1H), 5.07 (ddt, *J* = 17.1, 2.0, 1.5 Hz, 1H), 4.97 (ddt, *J* = 10.2, 2.0, 1.2 Hz, 1H), 4.58 (q, *J* = 1.1 Hz, 2H), 3.90 (d, *J* = 1.4 Hz, 2H), 3.30 (s, 3H), 3.07 (d, *J* = 7.3 Hz, 2H), 2.41 (dd, *J* = 9.2, 6.3 Hz, 2H), 2.34 – 2.20 (m, 2H), 1.70 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.55, 157.89, 157.85, 146.88, 138.29, 136.23, 136.14,

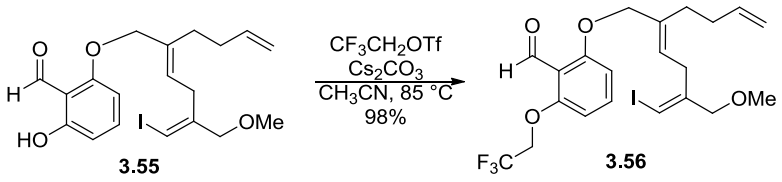
124.26, 115.13, 109.30, 106.96, 105.23, 103.73, 79.06, 74.86, 72.67, 58.14, 33.85, 32.38, 27.83, 25.74 (2C); IR (film) 3074, 2993, 2927, 2821, 1735, 1606, 1583, 1479, 1330, 1259, 1203, 1080, 918, 802, 761, 690 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{22}H_{28}IO_5$ $[M+H]^+$: 499.0976, found: 499.0982.



3.54 **3.55**

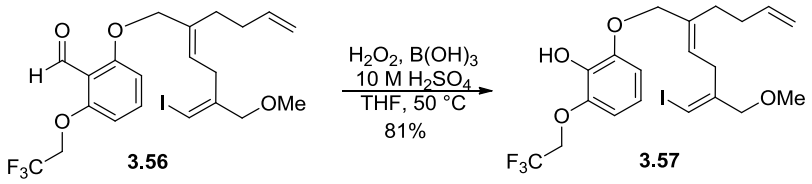
To a solution of acetonide (4.19 g, 8.41 mmol) in toluene (70 mL) cooled at -78 °C, DIBAL/PhMe (1.2M, 14.7 mL, 17.7 mmol) was added dropwise. After stirring at -78 °C for 3 h, the reaction was quenched by 10% Rochelle's salt solution (100 mL), diluted with ethyl acetate (200 mL), warmed to r.t. and vigorously stirred overnight. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (5 × 100 mL). The combined organic layers were washed with brine (200 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by column chromatography (10% ethyl acetate/hexanes) to afford a light yellow oil (3.48g, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.95 (s, 1H), 10.37 (d, *J* = 0.6 Hz, 1H), 7.38 (t, *J* = 8.4, 1H), 6.52 (dt, *J* = 8.4, 0.8 Hz, 1H), 6.37 (dd, *J* = 8.4, 0.8 Hz, 1H), 6.33 (dq, *J* = 1.3, 0.7 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.54 (ddt, *J* = 7.3, 6.4, 1.0 Hz, 1H), 5.07 (dq, *J* = 17.1, 1.6 Hz, 1H), 5.01 (ddt, *J* = 10.2, 1.9, 1.2 Hz, 1H), 4.52 (q, *J* = 1.0 Hz, 2H), 3.88 (d, *J* = 1.3 Hz, 2H), 3.29 (s, 3H), 3.07 (d, *J* = 7.3 Hz, 2H), 2.42 – 2.33 (m, 2H), 2.31 – 2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.32, 163.80, 161.75, 146.60, 138.45, 137.84, 136.17, 125.64, 115.49, 111.18,

110.05, 102.27, 79.70, 75.01, 72.65, 58.10, 33.86, 32.45, 28.00; IR (film) 3074, 3061, 2926, 2887, 1639, 1618, 1456, 1240, 1074, 914, 783, 717 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{19}H_{23}INaO_4$ $[M+Na]^+$: 465.0533, found: 465.0542.



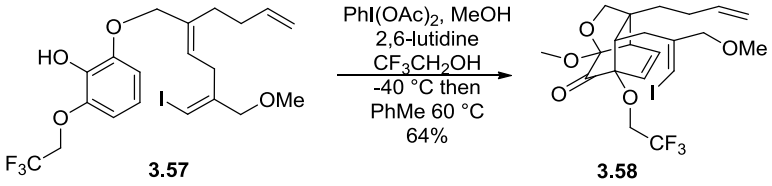
In a high-pressure flask was charged phenol (9.94 g, 22.5 mmol), cesium carbonate (7.33 g, 22.5 mmol), 2, 2, 2-trifluoroethyl trifluoromethanesulfonate (4.86 mL, 33.7 mmol) and dry acetonitrile (112 mL). The flask was flushed with N_2 for 5 minutes, capped and heated at 85 °C (bath temperature) for 2.0 h. The reaction solution gradually turned from light yellow to colorless. After cooling to r.t., the reaction mixture was diluted with ethyl acetate (150 mL) and filtered through a Celite pad. The filtrate was washed with saturated $NaHCO_3$ solution (3 × 100 mL) and brine (150 mL), dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to afford a light yellow oil (11.5 g, 98% yield). ^1H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, 1H), 7.43 (t, *J* = 8.4 Hz, 1H), 6.70 (d, *J* = 8.4, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.31 (td, *J* = 1.4, 0.6 Hz, 1H), 5.85 (ddt, *J* = 17.1, 10.2, 6.6 Hz, 1H), 5.58 (tt, *J* = 7.3, 1.1 Hz, 1H), 5.06 (dq, *J* = 17.1, 1.6 Hz, 1H), 4.99 (ddt, *J* = 10.2, 1.9, 1.2 Hz, 1H), 4.54 (q, *J* = 1.1 Hz, 2H), 4.42 (q, *J* = 8.1 Hz, 2H), 3.88 (d, *J* = 1.4 Hz, 2H), 3.29 (s, 3H), 3.06 (d, *J* = 7.3 Hz, 2H), 2.42 – 2.34 (m, 2H), 2.29 – 2.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 188.30, 161.38, 159.50, 146.70, 138.00, 136.15, 135.58, 125.07, 123.25 55 (q, *J* = 278.72 Hz), 116.08, 115.31,

107.77, 106.89, 79.37, 74.92, 72.84, 67.37 (q, J = 35.8 Hz), 58.09, 33.84, 32.36, 27.84; IR (film) 3076, 2978, 2927, 2877,2823, 2779, 1693, 1598, 1473, 1288, 1246, 1166, 1122, 777 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{24}F_3INaO_4$ $[M+Na]^+$: 547.0564, found: 547.0566.



In a high-pressure flask, 10 M sulfuric acid (3.9 mL, 39.3 mmo) was added to a suspension of boric acid (1.21 g, 19.6 mmol) in THF (30 mL) with stirring. Heat was generated during addition. After the flask had been cooled to r.t. in air, hydrogen peroxide (30 wt% in water, 0.98 mL, 8.65 mmol) was added slowly. After stirring at r.t. for 1.0 h, phenyl aldehyde (2.06 g, 3.93 mmol) in THF (10 mL) was added. The high-pressure flask was capped and immersed in 50 °C oil bath and heated for 4.0h. The reaction mixture turned from colorless to light yellow gradually. After the reaction was cooled to r.t., ethyl acetate (100 mL) was added and the mixture was washed with water (3 × 50 mL) and brine (50 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (10% ethyl acetate/hexanes) to yield a colorless oil (1.63 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, J = 8.3, 8.3 Hz, 1H), 6.65 (dd, J = 8.3, 1.4 Hz, 1H), 6.62 (dd, J = 8.3, 1.4 Hz, 1H), 6.31 (td, J = 1.3, 0.6 Hz, 1H), 5.85 (ddt, J = 17.1, 10.2, 6.5 Hz, 1H), 5.57 (s, 1H), 5.51 (tt, J = 7.3, 1.0 Hz, 1H), 5.07 (dq, J = 17.1, 1.4 Hz, 1H), 5.00 (ddt, J = 10.2, 1.9, 1.1 Hz, 1H), 4.52 (q, J = 1.0 Hz, 2H), 4.43

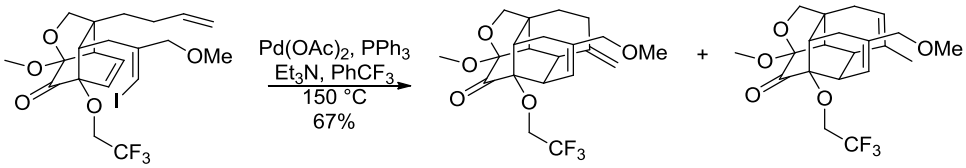
(q, J = 8.3 Hz, 2H), 3.84 (d, J = 1.3 Hz, 2H), 3.27 (s, 3H), 3.05 (d, J = 7.3, 2H), 2.40 – 2.31 (m, 2H), 2.30 – 2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.99, 146.65, 145.27, 138.00, 136.78, 136.64, 125.52, 123.55 (q, J = 278.72 Hz), 119.21, 115.38, 110.01, 108.54, 79.46, 74.90, 73.42, 67.84 (q, J = 35.3 Hz), 58.03, 33.87, 32.52, 27.90; IR (film) 3535, 3076, 2978, 2931, 2823, 1612, 1479, 1280, 1163, 1087, 1031, 966, 914, 777, 717 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{20}H_{24}F_3INaO_4$ $[M+Na]^+$: 535.0564, found: 535.0570.



3.57 **3.58**

To a solution of phenol (440.7 mg, 0.860 mmol) and 2,6-lutidine (0.5 mL, 4.30 mmol) in 2,2,2-triflouroethanol (76 mL) was added a solution of iodobenzene diacetate (290.9 mg, 0.903 mmol) in MeOH (10 mL) dropwise at -40 °C (acetonitrile/dry ice bath). After the addition was completed, the reaction was stirred at the same temperature for 1.0 h then transferred via cannula to pre-heated (70 °C) toluene (340 mL) in a 1 L 3-neck round-bottom flask equipped with a condenser. The resultant solution was stirred at 60 °C for 16 h while the reaction solution turned from yellow to light yellow gradually. After that period of time, the reaction was cooled to r.t., the solvent was removed on rotovap and the residue was placed under vacuum for a few hours to remove residual 2, 6-lutidine. Purification of the crude product by column chromatography (10-15% ethyl acetate/hexanes) gave a light yellow oil, 298.2 mg (64% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.27 (m, 2H), 5.77 (ddt, J = 17.1, 10.2,

6.3 Hz, 1H), 5.05 (dq, *J* = 17.1, 1.7 Hz, 1H), 5.00 (dq, *J* = 10.2, 1.5 Hz, 1H), 4.31 (dq, *J* = 11.3, 8.6 Hz, 1H), 4.13 (dq, *J* = 11.3, 8.6 Hz, 1H), 4.09 (d, *J* = 8.3 Hz, 1H), 4.04 (dd, *J* = 12.2, 0.9 Hz, 1H), 3.99 (dd, *J* = 12.2, 1.3 Hz, 1H), 3.85 (d, *J* = 8.3 Hz, 1H), 3.53 (s, 3H), 3.26 (s, 3H), 3.14 (dd, *J* = 5.5, 3.0 Hz, 1H), 2.81 (t, *J* = 7.1 Hz, 1H), 2.47 (ddd, *J* = 15.6, 6.6, 1.3 Hz, 1H), 2.35 (ddd, *J* = 15.6, 7.7, 1.1 Hz, 1H), 2.11 (dddt, *J* = 13.1, 7.8, 6.3, 1.5 Hz, 2H), 1.63 – 1.55 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.95, 146.95, 137.48, 129.97, 128.60, 123.64 (q, *J* = 277.5 Hz), 115.50, 99.64, 86.83, 80.72, 78.18, 75.50, 63.59 (q, *J* = 35.1 Hz), 57.68, 51.93, 50.24, 47.04, 45.38, 32.53, 30.73, 29.48; IR (film) 3074, 2976, 2937, 2893, 1755, 1641, 1454, 1284, 1161, 1093, 968, 889, 783, 688 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{27}F_3IO_5$ $[M+H]^+$: 543.0850, found: 543.0841.



3.58 **3.63** **3.64**

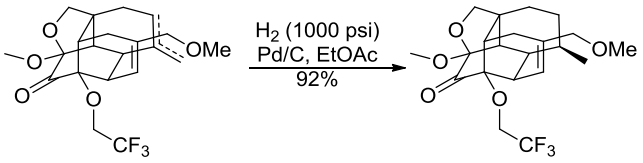
In a high-pressure flask charged with vinyl iodide (600 mg, 1.11 mmol) in trifluorotoluene (110 mL) was added triphenylphosphine (349.4 mg, 1.33 mmol) and triethylamine (0.77 mL, 5.55 mmol). The solution was purged with N_2 for 30 min and palladium (II) acetate (24.8 mg, 0.111 mmol) was added. After addition, the solution was purged with N_2 again for 30 min before the flask was capped and immersed in 150 °C oil bath. The reaction solution was stirred at 150 °C for 2 h and turned from light yellow to yellow over time. After cooling to r.t. the reaction mixture was filtered through a Celite pad and the filtrate was concentrated. The residue was purified by

column chromatography (10-15% ethyl acetate/hexanes) to afford two white solids, the higher R_f product being *exo*-olefin **3.63** (257.6 mg, 56% yield) and the lower R_f product being *endo*-olefin **3.64** (50.6 mg, 11% yield).

Exo-olefin **3.63**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.58 (dq, *J* = 7.1, 1.5 Hz, 1H), 4.83 (m, 1H), 4.77 (tt, *J* = 1.7, 0.9 Hz, 1H), 4.10 (dq, *J* = 10.7, 8.6 Hz, 1H), 3.89 (d, *J* = 12.3 Hz, 1H), 3.86 (dq, *J* = 10.7, 8.6 Hz, 1H), 3.83 (d, *J* = 7.4 Hz, 1H), 3.75 (d, *J* = 12.3 Hz, 1H), 3.71 (d, *J* = 7.4 Hz, 1H), 3.59 (s, 3H), 3.29 (s, 3H), 3.21 (dd, *J* = 11.3, 2.8 Hz, 1H), 2.79 (ddd, *J* = 10.9, 7.1, 3.0 Hz, 1H), 2.51 (dt, *J* = 5.7, 2.5 Hz, 1H), 2.42 – 2.26 (m, 3H), 2.21 (dd, *J* = 17.1, 8.1 Hz, 1H),), 2.08 (dd, *J* = 13.7, 7.7 Hz, 1H), 1.91 (d, *J* = 2.8 Hz, 1H), 1.48 (ddd, *J* = 13.7, 12.3, 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.99, 145.34, 137.70, 123.82 (q, *J* = 277.6 Hz), 119.42, 113.29, 103.14, 82.85, 80.05, 76.02, 63.05 (q, *J* = 34.8 Hz), 58.23, 52.19, 48.39, 45.45, 40.15, 37.72, 36.11, 28.24, 28.03, 24.88; IR (film) 3072, 2978, 2922, 2873, 1749, 1639, 1462, 1284, 1161, 1107, 972, 896, 734, 682 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{26}F_3O_5$ $[M+H]^+$: 415.1727, found: 415.1729.

Endo-olefin **3.64**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.55 (dt, *J* = 6.5, 1.6 Hz, 1H), 5.35 (ddd, *J* = 4.3, 2.8, 1.5 Hz, 1H), 4.14 (dq, *J* = 10.7, 8.5 Hz, 1H), 3.89 (d, *J* = 7.3 Hz, 1H), 3.88 (dq, *J* = 10.7, 8.5 Hz, 1H), 3.84 (d, *J* = 7.3 Hz, 1H), 3.79 (s, 2H), 3.61 (s, 3H), 3.24 (s, 3H), 2.85 – 2.71 (m, 2H), 2.45 – 2.34 (m, 2H), 2.24 (d, *J* = 2.8 Hz, 1H), 2.26 – 2.16 (m, 1H), 2.11 – 2.01 (m, 2H), 1.54 (dt, *J* = 2.8, 1.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.66, 138.57, 137.60, 123.82 (q, *J* = 277.6 Hz), 121.09, 117.78, 103.15, 82.36, 79.61, 76.01, 63.10 (q, *J* = 34.8 Hz), 57.33, 52.17, 45.61,

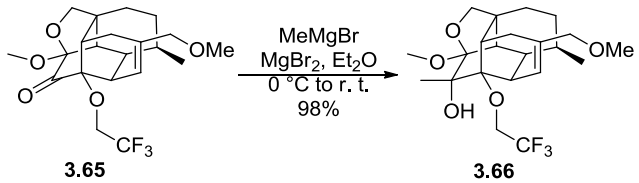
44.51, 38.24, 36.84, 36.09, 30.43, 25.01, 24.83; IR (film) 2929, 2845, 1749, 1454, 1284, 1157, 1107, 1066, 993, 883, 844, 736 cm^{-1} ; HRMS (MALDI) *m/z* calcd. for $C_{21}H_{25}F_3O_5Li$ $[M+Li]^+$: 421.1809, found: 421.1804.



3.63/3.64 **3.65**

In a 4-mL clear vial, palladium on carbon (10 wt%, 6.9 mg, 0.00647 mmol) was added to a solution of diene (exo- or endo-olefin form the previous step, 26.8 mg, 0.0647 mmol) in ethyl acetate (2.0 mL). Six of this vial were placed in a hydrogenation bomb and stirred at r.t. under 1000 psi H_2 for 8.0 h. The reaction mixtures were filtered through a Celite pad and the filtrates were combined and concentrated to afford a white solid (161.0 mg, 92% yield). This solid was used without further purification. (Note: The hydrogenation of the endo-olefin usually requires high pressure, however for the exo-olefin, the pressure requirement varies depending on the suppliers and batches of the palladium catalyst. In some cases the reaction was conducted under a hydrogen balloon.) ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 7.0, 1.7 Hz, 1H), 4.10 (dq, *J* = 10.7, 8.6 Hz, 1H), 3.88 (d, *J* = 12.8, 1H), 3.79 (dq, *J* = 10.7, 8.6 Hz, 1H), 3.79 (d, *J* = 7.3 Hz, 1H), 3.77 (d, *J* = 12.8, 1H), 3.71 (d, *J* = 7.3 Hz, 1H), 3.61 (s, 2H), 3.32 (s, 3H), 2.76 (ddd, *J* = 10.7, 7.3, 3.1 Hz, 1H), 2.50 – 2.43 (m, 2H), 2.29 (dd, *J* = 19.0, 7.7 Hz, 1H), 2.20 (dt, *J* = 19.0, 1.1 Hz, 1H), 2.09 (dd, *J* = 13.5, 6.0 Hz, 1H), 1.83 (d, *J* = 2.4 Hz, 1H), 1.67 (dddd, *J* = 12.8, 7.0, 5.8, 3.7 Hz, 1H), 1.63 – 1.54 (m, 1H), 1.47 – 1.42 (m, 1H), 1.42 – 1.35 (m, 2H), 1.12 (d, *J*

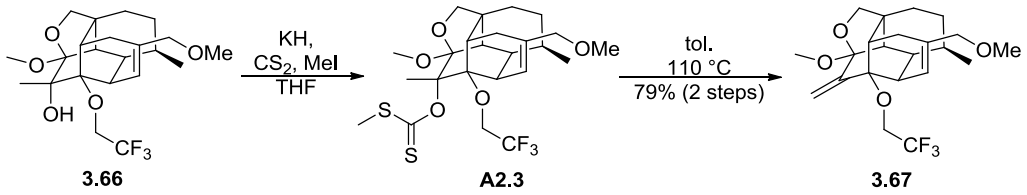
= 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.88, 137.96, 123.87 (d, *J* = 277.6 Hz), 118.91, 103.09, 82.92, 80.72, 76.00, 63.08 (q, *J* = 34.7 Hz), 58.48, 52.44, 51.13, 45.58, 37.76, 37.52, 35.94 (2C), 28.87, 25.77, 24.59, 21.18; IR (film) 2980, 2914, 2875, 2827, 1751, 1284, 1157, 1103, 1070, 975, 885, 732 cm^{-1} ; HRMS (MALDI) *m/z* calcd. for $C_{21}H_{27}F_3O_5Li$ $[M+Li]^+$: 423.1965, found: 423.1954.



3.65 **3.66**

Magnesium bromide diethyl etherate (1.59 g, 6.16 mmol) in a flask was dried by heating gently under vacuum. After the flask was cooled to r.t., anhydrous diethyl ether (15 mL) was added. Magnesium bromide dissolved in ether and two layers of liquid were resulted. Ketone (854.8 mg, 2.05 mmol) in diethyl ether (25 mL) was then added. A white cloudy suspension was formed with a sticky layer of oil on the bottom of the flask. The mixture was cooled to 0 °C with vigorous stirring. Grignard reagent (3.0 M, 2.06 mL, 6.18 mmol) was added dropwise while the suspension turned to a clear solution and the oil layer still existed. After the addition was completed, the reaction mixture was warmed to r.t. and stirred for 1.5 h, during that period of time a white precipitate formed again and the oil layer gradually disappeared. While the reaction was completed it was cooled to 0 °C, quenched by saturated NH_4Cl solution (30 mL) and diluted with water (30 mL) and ethyl acetate (50 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous

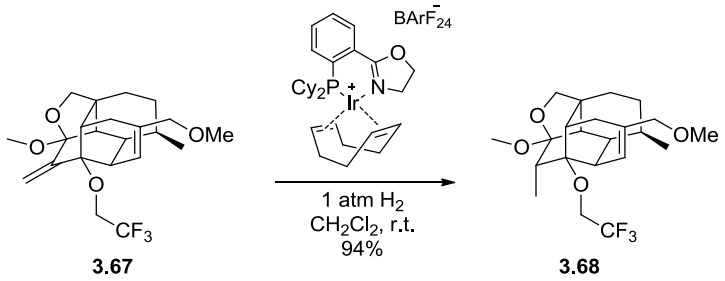
Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography (10% ethyl acetate/hexanes) to afford a colorless oil (868.8 mg, 98% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (dt, *J* = 7.2, 1.6 Hz, 1H), 4.17 (dq, *J* = 10.8, 8.8 Hz, 1H), 3.86 (ddd, *J* = 12.5, 1.5, 0.7 Hz, 1H), 3.75 (ddd, *J* = 12.5, 1.5, 0.7 Hz, 1H), 3.57 (d, *J* = 6.8 Hz, 1H), 3.48 (dq, *J* = 10.8, 8.8 Hz, 1H), 3.42 (d, *J* = 6.8 Hz, 1H), 3.34 (s, 3H), 3.31 (s, 3H), 3.12 (ddt, *J* = 10.6, 7.4, 3.1 Hz, 1H), 2.91 (s, 1H), 2.40 – 2.25 (m, 2H), 2.11 – 1.89 (m, 3H), 1.76 – 1.51 (m, 2H), 1.48 (d, *J* = 2.2 Hz, 1H), 1.34 – 1.20 (m, 2H), 1.23 (s, 3H), 1.11 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.88, 124.50 (q, *J* = 277.5 Hz), 120.44, 106.63, 82.18, 80.98, 78.53, 76.30, 62.82 (q, *J* = 33.9 Hz), 58.44, 49.59, 44.29, 44.04, 40.40, 37.87, 36.15, 28.75, 28.55, 26.12, 25.60, 21.45, 16.92; IR (film) 3552, 2981, 2933, 2912, 2872, 1463, 1375, 1282, 1165, 1147, 989, 862 cm^{-1} ; HRMS (MALDI) *m/z* calcd. for $C_{22}H_{31}F_3O_5Li$ $[M+Li]^+$: 439.2278, found: 439.2275.



Potassium hydride (30 wt% in mineral oil, 1.06 g, 7.95 mmol) was washed with dry pentane three times under N_2 then suspended in THF (10 mL). Alcohol (0.86 g, 1.99 mmol) in THF (10 mL) was added dropwise at 0 °C. After stirring at 0 °C for 2.0 h, freshly distilled carbon disulfide (1.20 mL, 19.9 mmol) was added dropwise. The reaction was stirred at 0 °C for 1.0 h and r.t. 6.0h. After that period of time, the reaction was cooled to 0 °C again and methyl iodide (1.24 mL, 19.9 mmol) was added

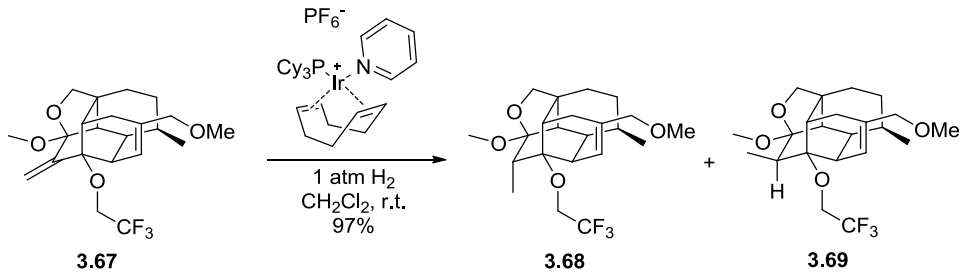
dropwise. The resultant mixture was allowed to warm up to r.t. and stirred for 12 h. The reaction was quenched by water (10 mL) at 0 °C and diluted with ethyl acetate (20 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated.

The crude product from the previous operation was dissolved in toluene (200 mL, 0.01 M) and heated at 110 °C for 2.0 h. After cooling to r.t. the reaction mixture was concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford a light yellow solid (0.65 g, 79% yield over 2 steps). (Note: To assure the success of the subsequent iridium catalyzed hydrogenation, this solid should be further purified by trituration with hexanes and filtration to remove the tiny amount of colored impurities.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 7.5, 1.4 Hz, 1H), 5.53 (d, *J* = 1.1 Hz, 1H), 5.14 (t, *J* = 0.9 Hz, 1H), 3.94 (dq, *J* = 10.8, 8.8 Hz, 1H), 3.91 (d, *J* = 12.5 Hz, 1H), 3.75 (d, *J* = 12.5Hz, 1H), 3.70 (dq, *J* = 10.8, 8.8 Hz, 1H), 3.66 (d, *J* = 7.1 Hz, 1H), 3.52 (d, *J* = 7.1 Hz, 1H), 3.39 (s, 3H), 3.30 (s, 3H), 2.48 – 2.39 (m, 1H), 2.32 – 2.12 (m, 4H), 2.03 (dd, *J* = 13.2, 5.5 Hz, 1H), 1.71 (d, *J* = 2.2 Hz, 1H), 1.68 – 1.50 (m, 2H), 1.44 – 1.25 (m, 2H),1.07 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, CDCl3) δ 149.23, 135.85, 124.15 (q, *J* = 277.3 Hz), 122.80, 106.65, 105.52, 82.11, 79.29, 76.29, 61.60 (q, *J* = 34.3 Hz), 57.82, 49.53, 46.57, 44.69, 41.17, 38.40, 37.42, 36.78, 29.00, 26.06, 24.84, 21.30; IR (film) 2980, 2916, 2873, 1276, 1161, 1103, 1083, 964, 866 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{22}H_{30}F_3O_4$ $[M+H]^+$: 415.2091, found: 415.2086.



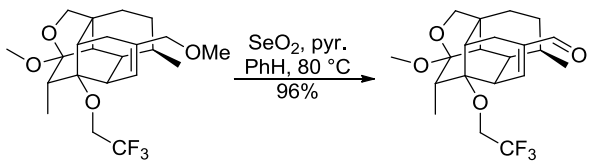
3.67 **3.68**

To a solution of diene (464.0 mg, 1.12 mmol) in CH_2Cl_2 (11.2 mL), iridium catalyst[3] (16.9 mg, 0.0112 mmol) was added in one portion. Hydrogen was bubbled into the resultant pink solution for 5.0 min. The color was quickly discharged and the solution turned to light yellow. The reaction was stirred at r.t. under H_2 balloon for 22 h. After removal of solvent, the residue was purified by column chromatography (15% ethyl acetate/hexanes) to afford a white solid (439.4 mg, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (dt, *J* = 7.2, 1.5 Hz, 1H), 3.88 (d, *J* = 12.1 Hz, 1H), 3.74 (d, *J* = 12.1 Hz, 1H), 3.72 (dq, *J* = 10.8, 8.8 Hz, 1H), 3.63 (dq, *J* = 10.8, 8.8 Hz, 1H), 3.58 (d, *J* = 6.9 Hz, 1H), 3.40 (d, *J* = 6.9 Hz, 1H), 3.33 (s, 3H), 3.29 (s, 3H), 2.56 (ddd, *J* = 10.5, 7.2, 2.8 Hz, 1H), 2.28 (ddd, *J* = 11.3, 3.5, 2.1 Hz, 1H), 2.19 (q, *J* = 7.2 Hz, 1H), 2.15 – 2.08 (m, 3H), 1.95 (dd, *J* = 13.4, 6.3 Hz, 1H), 1.74 – 1.62 (m, 1H), 1.58 (dddd, *J* = 12.5, 7.0, 5.5, 3.5 Hz, 1H), 1.41 (d, *J* = 2.1 Hz, 1H), 1.37 – 1.18 (m, 2H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.87, 124.18 (q, *J* = 277.7 Hz), 123.50, 107.97, 81.39, 79.85, 76.45, 60.58 (q, *J* = 34.4 Hz), 57.83, 49.98, 46.49, 44.15, 43.46, 39.06, 37.46, 36.06, 33.16, 28.19, 26.21, 25.25, 21.40, 9.02; IR (film) 2980, 2926, 2875, 1463, 1384, 1280, 1161, 1109, 1020, 862, 678 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{22}H_{32}F_3O_4$ $[M+H]^+$: 417.2247, found: 417.2250.



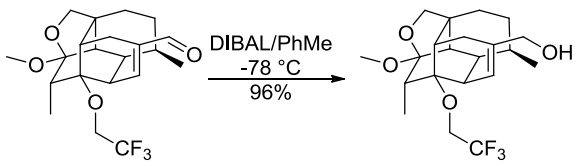
3.67 **3.68** **3.69**

To a solution of diene (138.2 mg, 0.334 mmol) in CH_2Cl_2 (6.7 mL) Crabtree catalyst (13.4 mg, 0.0167 mmol) was added in one portion. Hydrogen was bubbled into the resultant pink solution for 5.0 min. The color was quickly discharged and the solution turned to bright yellow. The reaction was stirred at r.t. under H_2 balloon for 2 h. After concentration, the residue was purified by column chromatography (15% ethyl acetate/hexanes) to afford two white solids: **3.69** (higher R_f, 74.5 mg, 54% yield) and **3.68** (lower R_f, 60.2 mg, 43% yield). Undesired diastereomer **3.69**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.73 (dt, *J* = 6.9, 1.6 Hz, 1H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.74 (d, *J* = 12.7 Hz, 1H), 3.59 (d, *J* = 6.9 Hz, 1H), 3.54 (dq, *J* = 10.1, 8.3 Hz, 1H), 3.45 (d, *J* = 6.9 Hz, 1H), 3.39 (dq, *J* = 10.1, 8.3 Hz, 1H), 3.30 (s, 3H), 3.30 (s, 3H), 2.36 (ddd, *J* = 10.4, 6.8, 3.0 Hz, 1H), 2.33 – 2.25 (m, 2H), 2.11 (dd, *J* = 7.6, 3.1 Hz, 1H), 2.05 (d, *J* = 18.6 Hz, 1H), 1.97 (m, 2H), 1.64 – 1.56 (m, 2H), 1.51 (d, *J* = 2.2 Hz, 1H), 1.35 – 1.24 (m, 2H), 1.10 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.08, 124.18 (q, *J* = 277.6 Hz), 119.84, 108.96, 82.07, 78.44, 76.15, 60.94 (q, *J* = 34.3 Hz), 58.28, 49.20, 45.14, 43.60, 43.47, 38.99, 37.51, 36.29, 36.07, 28.93, 26.19, 25.35, 21.39, 6.89; IR (film) 2981, 2911, 2875, 2829, 1462, 1451, 1279, 1165, 1130, 1120, 1088, 1013, 970 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{22}H_{32}F_3O_4$ $[M+H]^+$: 417.2247, found: 417.2242.



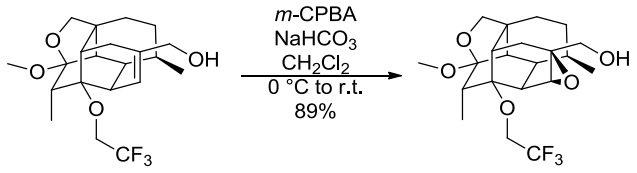
3.68 **3.70**

A high-pressure tube charged with a solution of vinyl ether (110 mg, 0.264 mmol) in benzene (5.0 mL), selenium dioxide (146.5 mg, 1.32 mmol) and pyridine (0.21 mL, 2.64 mmol) was sealed and heated to 80 °C. The reaction solution turned from colorless to light yellow and a pink precipitate formed on the flask wall and turned black over time. After 42 h the reaction mixutre was cooled to r.t. and filtered through a Celite pad. The filtrate was concentrated and purified by column chromatography (20% ethyl acetate/hexanes) to afford a white solid (101.8 mg, 96% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.48 (s, 1H), 7.00 (dt, *J* = 7.3, 1.8 Hz, 1H), 3.69 (dq, *J* = 11.0, 8.4 Hz, 1H), 3.63 (d, *J* = 7.1 Hz, 1H), 3.57 (dq, *J* = 10.9, 8.5 Hz, 1H), 3.44 (d, *J* = 7.2 Hz, 1H), 3.35 (s, 3H), 2.84 (ddd, *J* = 11.1, 7.3, 3.2 Hz, 1H), 2.50 – 2.44 (m, 2H), 2.28 (ddt, *J* = 19.5, 7.6, 1.1 Hz, 1H), 2.25 – 2.19 (m, 2H), 1.97 – 1.89 (m, 1H), 1.62 (ddt, *J* = 14.3, 7.0, 3.7 Hz, 1H), 1.47 (d, *J* = 2.1 Hz, 1H), 1.38 – 1.19 (m, 3H), 1.10 (d, *J* = 7.1 Hz, 3H), 0.99 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.87, 150.60, 142.77, 123.90 (q, *J* = 277.7 Hz), 107.71, 81.20, 79.90, 60.45 (q, *J* = 34.6 Hz), 50.09, 46.26, 44.17, 43.29, 38.08, 37.23, 36.92, 34.82, 27.96, 26.09, 21.62, 21.11, 8.95; IR (film) 2981, 2933, 2877, 1678, 1282, 1163, 1147, 1111, 1018, 731 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{28}F_3O_4$ $[M+H]^+$: 401.1934, found: 401.1936.



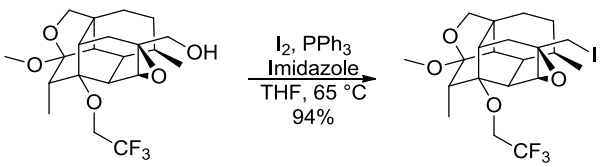
3.70 **3.71**

To a solution of aldehyde (156.6 mg, 0.391 mmol) in toluene (7.8 mL) was added DIBAL (1.0 M in toluene, 0.59 mL) dropwise at -78 °C. The reaction was stirred at -78 °C for 1.0 h then quenched by 15% Rochelle's salt solution (10 mL). The mixture was diluted with ethyl acetate (10 mL), warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (30% ethyl acetate/hexanes) to afford a white solid (151.3 mg, 96% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.79 (dt, *J* = 6.9, 1.5 Hz, 1H), 4.08 – 3.97 (m, 2H), 3.70 (dq, *J* = 10.9, 8.5 Hz, 1H), 3.62 (dq, *J* = 10.9, 8.5 Hz, 1H), 3.59 (d, *J* = 6.9 Hz, 1H), 3.41 (d, *J* = 6.9 Hz, 1H), 3.34 (s, 3H), 2.55 (ddd, *J* = 10.7, 7.1, 2.8 Hz, 1H), 2.29 (dt, *J* = 11.2, 2.7 Hz, 1H), 2.22 – 2.11 (m, 4H), 1.96 (dd, *J* = 13.7, 6.3 Hz, 1H), 1.70 – 1.54 (m, 2H), 1.42 (d, *J* = 2.1 Hz, 1H), 1.37 – 1.24 (m, 3H), 1.09 (d, *J* = 6.9 Hz, 3H), 0.97 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.42, 124.26 (q, *J* = 277.8 Hz), 121.84, 108.07, 81.41, 79.79, 66.78, 60.60 (q, *J* = 34.2 Hz), 50.05, 46.42, 44.11, 43.62, 38.89, 37.47, 36.01, 33.04, 28.22, 26.35, 24.81, 21.45, 9.04; IR (film) 3429, 2980, 2929, 2875, 1463, 1280, 1161, 1116, 1055, 1037, 1018, 862, 734 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}F_3O_4$ $[M+H]^+$: 403.2091, found: 403.2089.



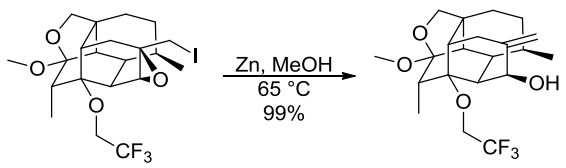
3.71 **3.72**

A mixture of allylic alcohol (82.2 mg, 0.204 mmol), $NaHCO_3$ (51.4 mg, 0.612 mmol) in CH_2Cl_2 (4.0 mL) was cooled to 0 °C, to which *m*-CPBA (70-75 wt% in water, 75.6 mg, 0.306 mmol) was added in one portion. The reaction was allowed to warm to r.t. naturally and stirred for total 15 h. After that period of time, the reaction mixture became cloudy, and then water (2 mL) and ethyl acetate (10 mL) were added. The organic phase was separated and washed with saturated $NaHSO_3$ (3 × 2 mL), saturated $NaHCO_3$ (3 × 2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by column chromatography (50% ethyl acetate/hexanes) to afford a white solid (75.8 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.82 (dd, *J* = 12.7, 2.4 Hz, 1H), 3.77 – 3.59 (m, 4H), 3.51 (d, *J* = 6.9 Hz, 1H), 3.35 (d, *J* = 6.9 Hz, 1H), 3.32 (s, 3H), 2.70 (dt, *J* = 10.8, 2.7 Hz, 1H), 2.41 (dt, *J* = 10.8, 2.4 Hz, 1H), 2.12 (q, *J* = 7.2 Hz, 1H), 2.00 (dd, *J* = 16.0, 6.8 Hz, 1H), 1.96 – 1.89 (m, 2H), 1.86 – 1.75 (m, 3H), 1.69 – 1.47 (m, 3H), 1.47 – 1.44 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.21 (q, *J* = 278.1 Hz), 107.00, 81.22, 81.00, 63.38, 60.20 (q, *J* = 34.7 Hz), 58.36, 56.38, 50.12, 49.06, 44.14, 44.01, 39.52, 37.27, 34.17, 32.38, 27.00, 26.90, 23.21, 21.70, 8.97; IR (film) 3449, 2932, 2880, 1736, 1464, 1279, 1166, 1149, 1118, 1049, 1012, 964, 931, 782 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}F_3O_5$ $[M+H]^+$: 419.2040, found: 419.2032.



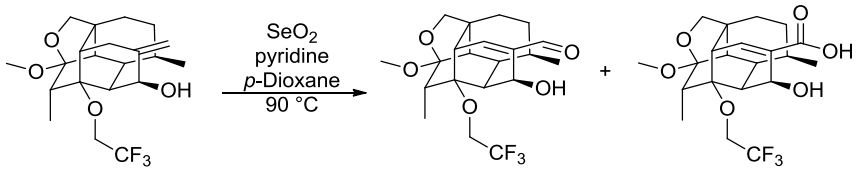
3.72 **3.74**

To a solution of alcohol (75.8 mg, 0.181 mmol) in THF (3.6 mL) triphenylphosphine (71.1 mg, 0.272 mmol), imidazole (24.4 mg, 0.363 mmol) and iodine (69.1 mg, 0.272 mmol) were added in sequence. The reaction mixture were stirred at 65 °C for 16 h then cooled to r.t. and diluted with ethyl acetate (10 mL). After washing with 10% $Na_2S_2O_3$ (5 mL) and brine (5 mL) the solution was dried over anhydrous Na_2SO_4, filtered and concentrated. Purification of the crude product by column chromatography (20% ethyl acetate/hexanes) gave a white solid (90.0 mg, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 – 3.57 (m, 5H), 3.51 (d, *J* = 6.9 Hz, 1H), 3.39 – 3.32 (m, 1H), 3.31 (s, 3H), 3.10 (d, *J* = 10.1 Hz, 1H), 2.59 (dt, *J* = 10.9, 2.7 Hz, 1H), 2.41 (dt, *J* = 10.8, 2.4 Hz, 1H), 2.31 – 2.20 (m, 1H), 2.10 (q, *J* = 7.2 Hz, 1H), 2.00 – 1.74 (m, 3H), 1.74 – 1.59 (m, 1H), 1.58 – 1.42 (m, 3H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.14 (q, *J* = 278.3 Hz), 106.94, 81.11, 80.26, 63.74, 60.26 (q, *J* = 34.7 Hz), 55.97, 50.16, 49.06, 44.10, 44.08, 40.16, 37.34, 34.02, 33.61, 27.43, 27.11, 26.81, 21.80, 15.12, 9.05; IR (film) 2975, 2932, 2878, 1462, 1279, 1150, 1116, 1014, 965, 732 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{29}F_3IO_4$ $[M+H]^+$: 529.1057, found: 529.1058.



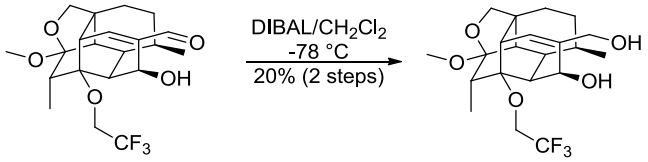
3.74 **3.75**

In a high-pressure tube a mixture of epoxide (90.0 mg, 0.170 mmol), zinc powder (111.0 mg, 1.70 mmol, used as received from commercial supplier and no further treatment) in MeOH (8.5 mL) was heated at 65 °C for 20 h then cooled to r.t. The unreacted zinc solid was filtered off over a Celite pad and the filtrate was concentrated then purified by column chromatography (15% ethyl acetate/hexanes) to afford a white solid (68.4 mg, 99% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.32 (s, 1H), 5.12 (s, 1H), 4.78 (d, *J* = 11.7 Hz, 1H), 3.79 (dq, *J* = 11.0, 8.3 Hz, 1H), 3.66 (dq, *J* = 11.0, 8.3 Hz, 1H), 3.51 (d, *J* = 6.9 Hz, 1H), 3.37 (d, *J* = 6.9 Hz, 1H), 3.31 (s, 2H), 3.06 (d, *J* = 11.7 Hz, 1H), 2.71 (dq, *J* = 18.8, 1.8 Hz, 1H), 2.67 – 2.59 (m, 1H), 2.51 (dd, *J* = 12.2, 3.1 Hz, 1H), 2.37 (dt, *J* = 12.2, 2.4 Hz, 1H), 2.17 (q, *J* = 7.2 Hz, 1H), 2.07 – 2.02 (m, 1H), 1.98 – 1.90 (m, 1H), 1.77 – 1.62 (m, 2H), 1.47 – 1.39 (m, 1H), 1.45 (d, *J* = 2.0 Hz, 1H), 1.33 (ddd, *J* = 14.0, 12.0, 6.9 Hz, 1H), 1.22 (d, *J* = 6.9 Hz, 3H), 1.01 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.94, 123.94 (q, *J* = 277.9 Hz), 114.97, 107.79, 83.16, 80.80, 68.70, 59.95 (q, *J* = 34.8 Hz), 50.14, 48.61, 43.77, 43.50, 40.32, 39.24, 37.66, 34.38, 28.61, 27.39, 26.35, 21.74, 9.05; IR (film) 3564, 2926, 2881, 2858, 1454, 1282, 1273, 1165, 1109, 1024, 979, 678 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}F_3O_4$ $[M+H]^+$: 403.2090, found: 403.2091.



3.75 **3.76** **3.77**

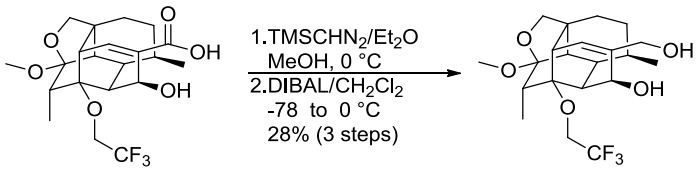
A mixture of allylic alcohol (15.0 mg, 0.0373 mmol), pyridine (0.03 mL, 0.373 mmol) and selenium dioxide (20.7 mg, 0.186 mmol) in *p*-dioxane (1.2 mL) was heated to 90 °C and stirred for 16 h. After cooling to r.t., the reaction mixture was filtered through a Celite pad and the filtrate was concentrated. The residue was dissolved in ethyl acetate (10 mL) and washed with saturated $NaHCO_3$ (3 × 5 mL) and brine (5 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated to afford the aldehyde product. The aqueous phase was acidified to pH 1.0 by 1 N HCl, and then extracted with ethyl acetate (3 × 10 mL). The extracts were combined and washed with brine (10 mL), dried over anhydrous Na2SO4, filtered and concentrated to afford the acid product. Both crude products were converted to alcohol and purified afterward.



3.76 **3.73**

The aforementioned crude aldehyde was dissolved in CH_2Cl_2 (0.30 mL) and cooled to -78 °C, DIBAL (1.0 M in CH_2Cl_2, 0.11 mL) was added dropwise. The reaction was stirred at -78 °C for 2 h then quenched by 10% Rochelle's salt solution (1 mL). The mixture was diluted with ethyl acetate (5 mL), warmed to r.t. and stirred

vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (40% ethyl acetate/hexanes) to provide a colorless oil (3.2 mg, 20% yield over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (d, *J* = 7.2 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.30 (m, 2H), 3.71 – 3.60 (dq, *J* = 10.7, 8.4 Hz, 1H), 3.62 (d, *J* = 7.1 Hz, 1H), 3.47 (dq, *J* = 10.7, 8.4 Hz, 1H), 3.33 (d, *J* = 7.1 Hz, 1H), 3.32 (s, 3H), 3.03 (d, *J* = 11.4 Hz, 1H), 2.56 – 2.46 (m, 2H), 2.36 (dt, *J* = 11.9, 2.6 Hz, 1H), 2.26 (dd, *J* = 7.2, 2.9 Hz, 1H), 2.18 (q, *J* = 7.2 Hz, 1H), 1.80 – 1.58 (m, 2H), 1.45 – 1.37 (m, 2H), 1.36 – 1.26 (m, 2H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.21, 123.91 (q, *J* = 277.6 Hz), 119.12, 107.66, 81.60, 80.29, 67.43, 65.33, 59.68 (q, *J* = 34.7 Hz), 50.23, 49.05, 44.03, 42.87, 42.19, 40.61, 37.03, 33.62, 28.26, 26.88, 22.16, 9.16; IR (film) 3553, 3441, 2975, 2927, 2878, 1281, 1165, 1110, 1017, 733 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}F_3O_5$ $[M+H]^+$: 419.2039, found: 419.2043.

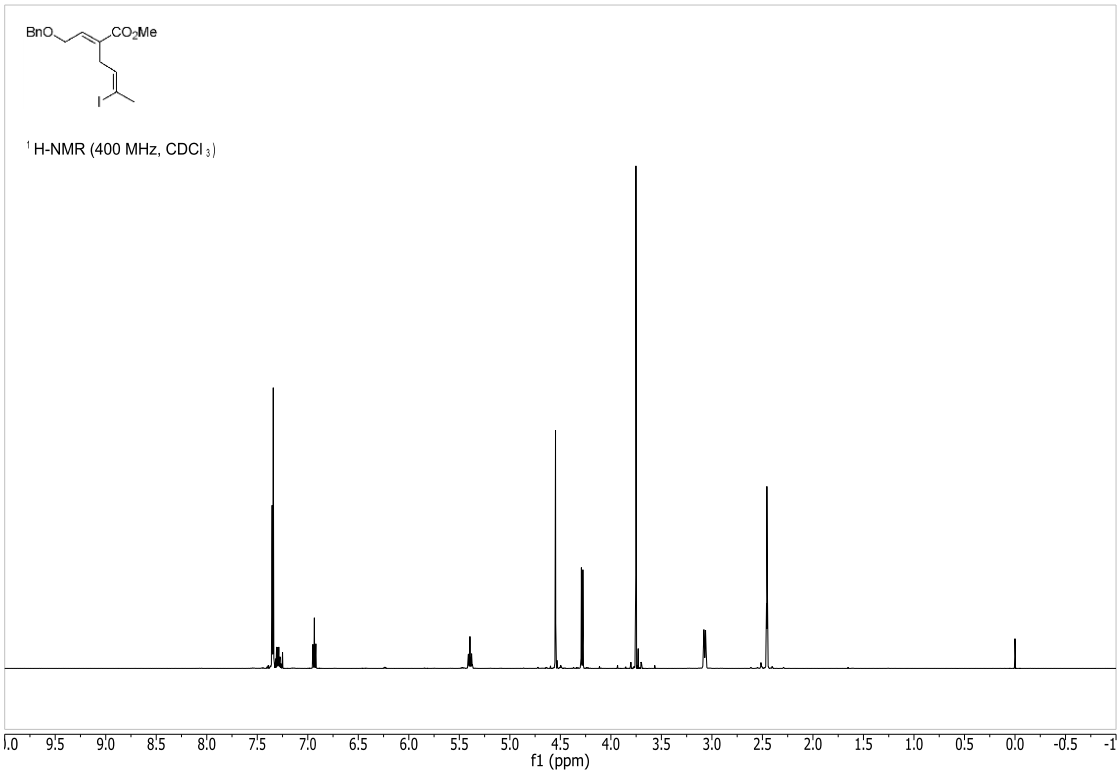


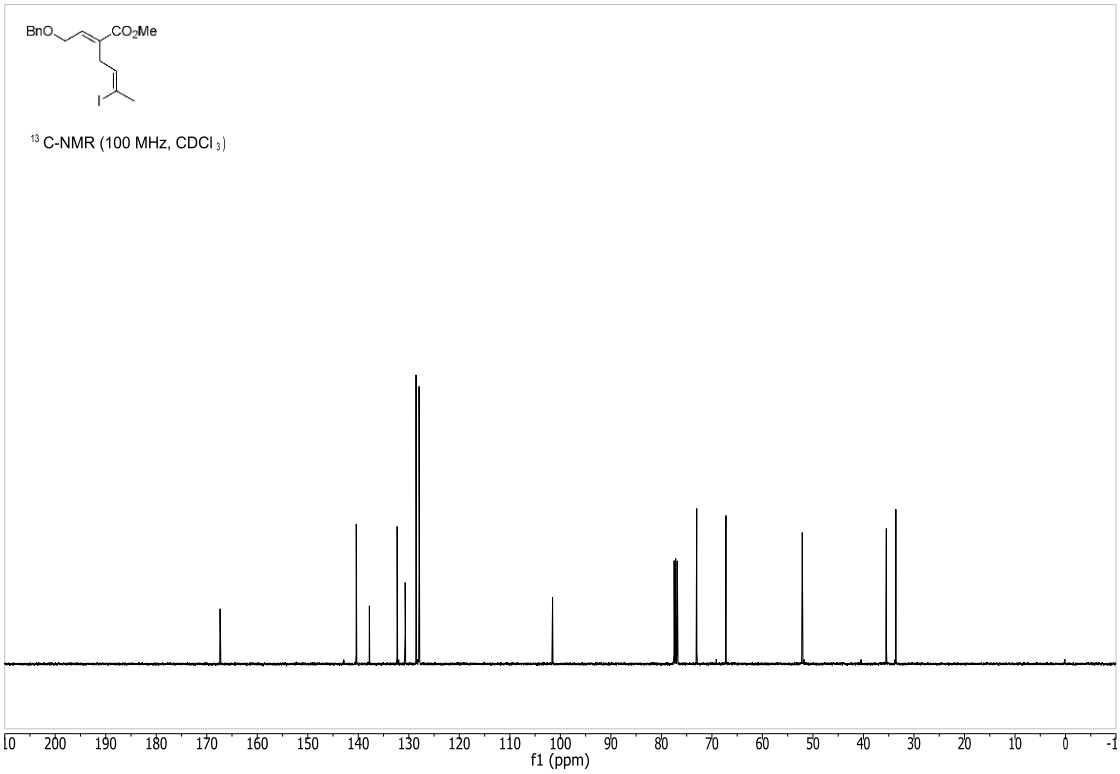
3.77 **3.73**

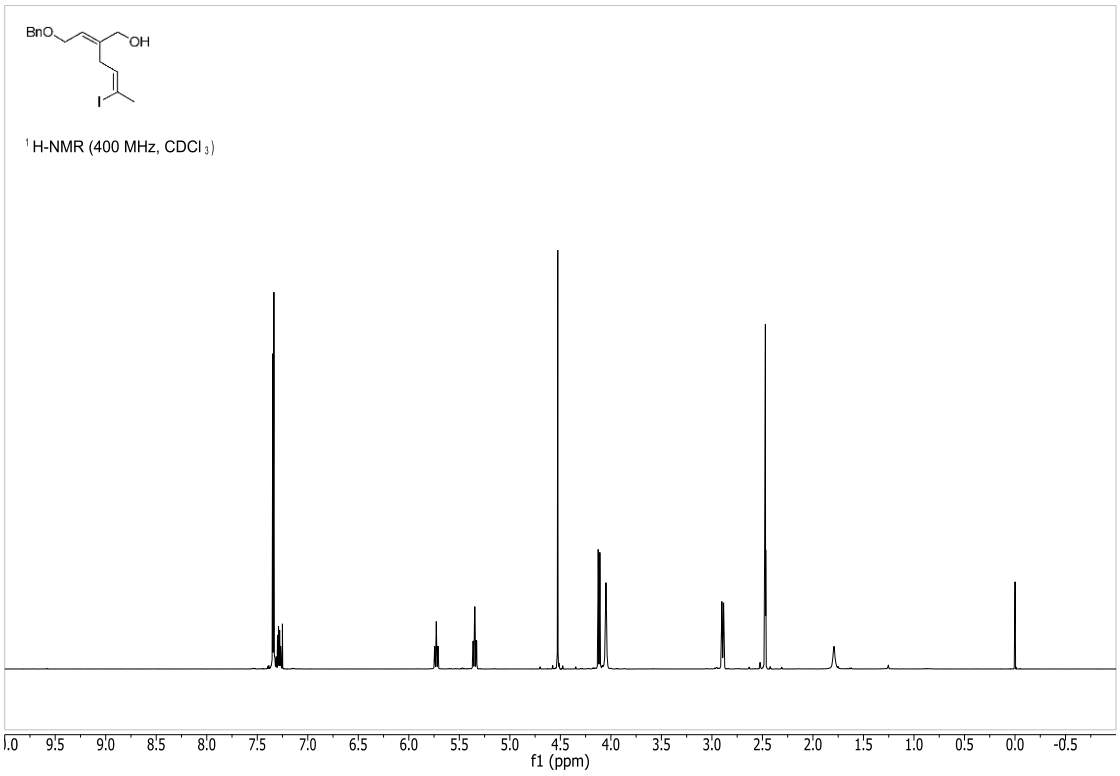
The aforementioned crude acid was dissolved in methanol (0.30 mL) and cooled to 0 °C, and then trimethylsilyldiazomethane (2.0 M in diethyl ether, 0.10 mL) was added dropwise. The reaction was stirred at 0 °C for 1 h then diluted with ethyl acetate and concentrated in vacuo. The residue was re-dissolved in CH_2Cl_2 (0.30 mL)

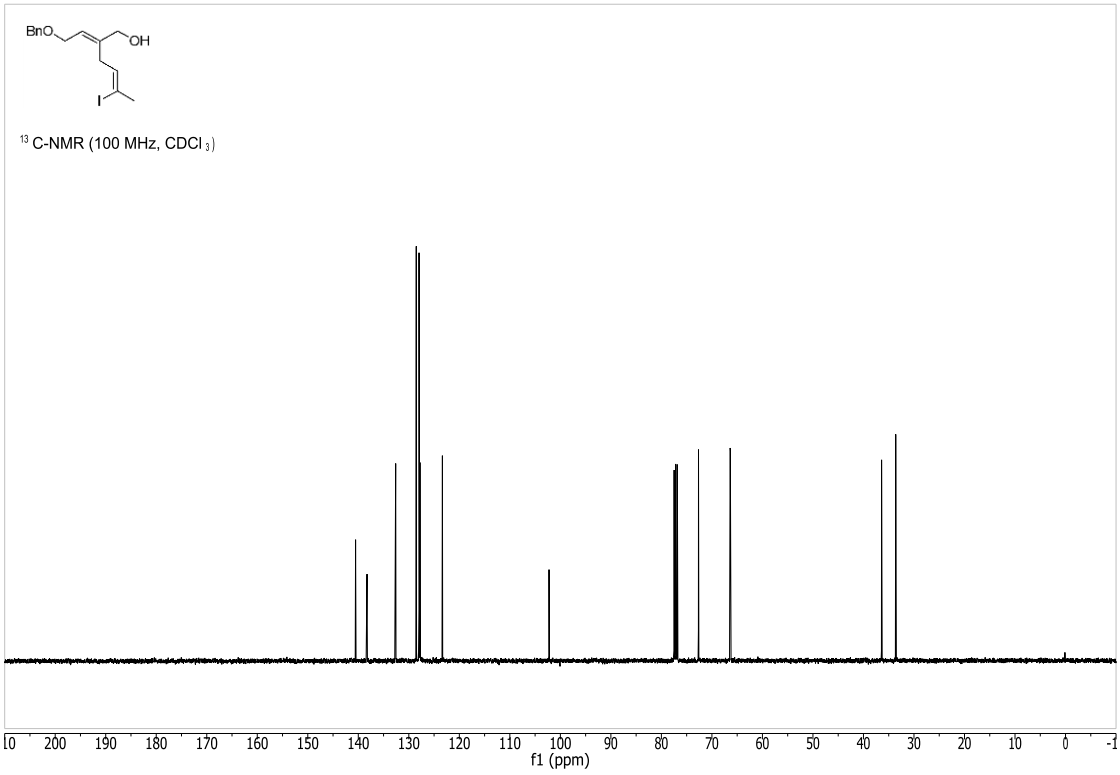
and cooled to -78 °C, DIBAL (1.0 M in CH_2Cl_2, 0.20 mL) was added dropwise. The reaction was stirred at -78 °C for 2 h then warmed to 0 °C and stirred for 1 h. The reaction was quenched by 10% Rochelle's salt solution (1 mL), diluted with ethyl acetate (5 mL), warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by flash column chromatography (40% ethyl acetate/hexanes) to provide the same alcohol (4.4 mg, 28% yield over 3 steps).

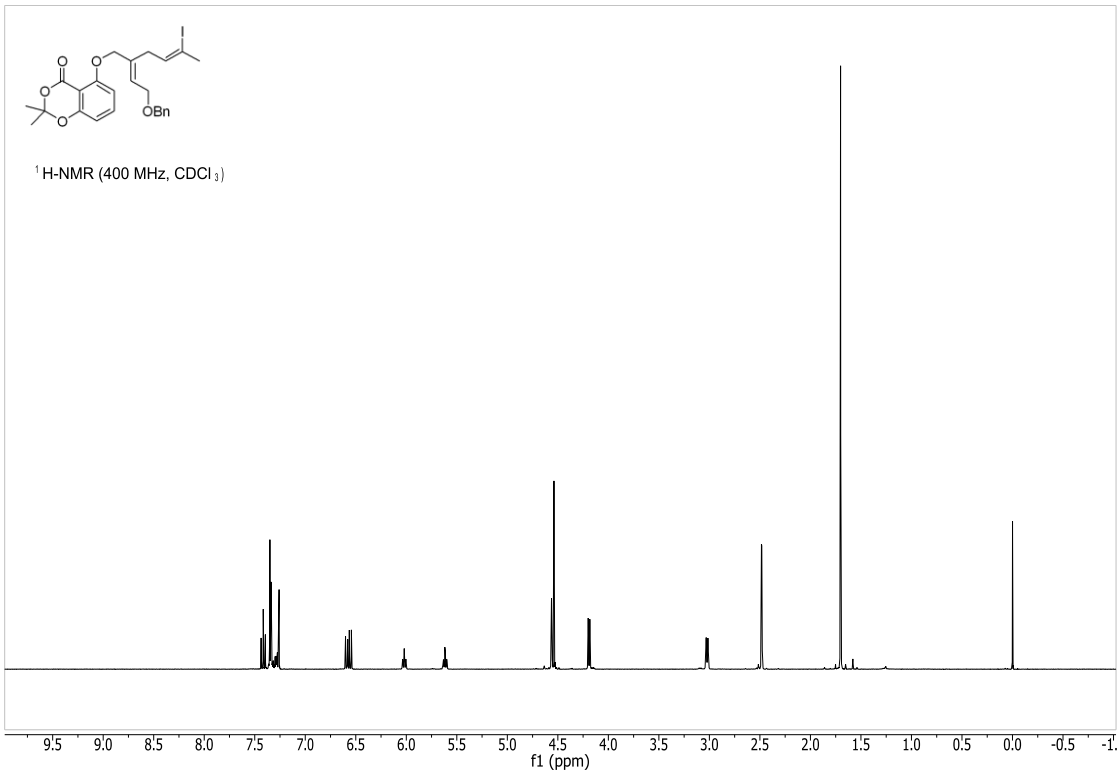
A2.2 ^{1}H and ^{13}C-NMR spectra for Chapter 3

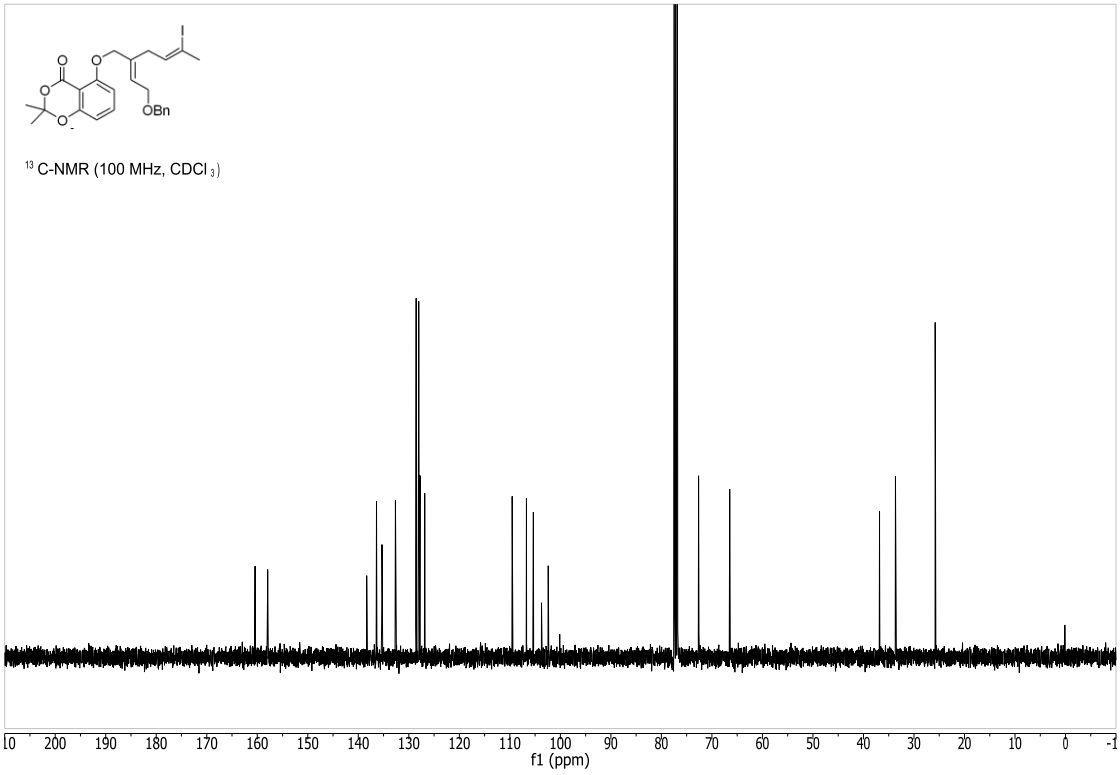


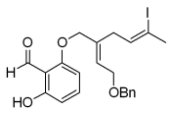



BnO
OH
I
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

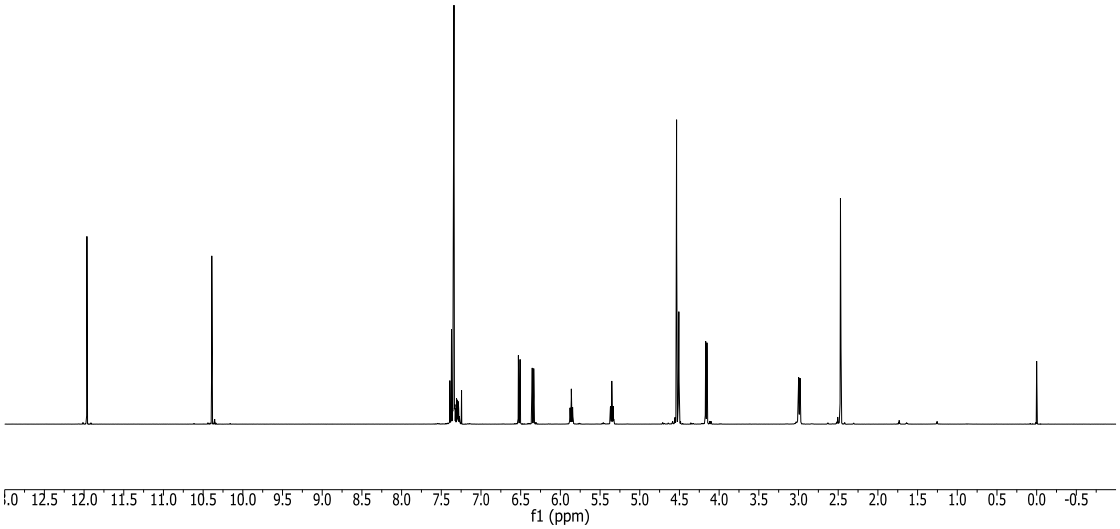

BnO
OH
I
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

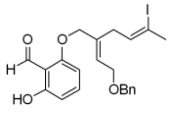

OBn
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)


OBn
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

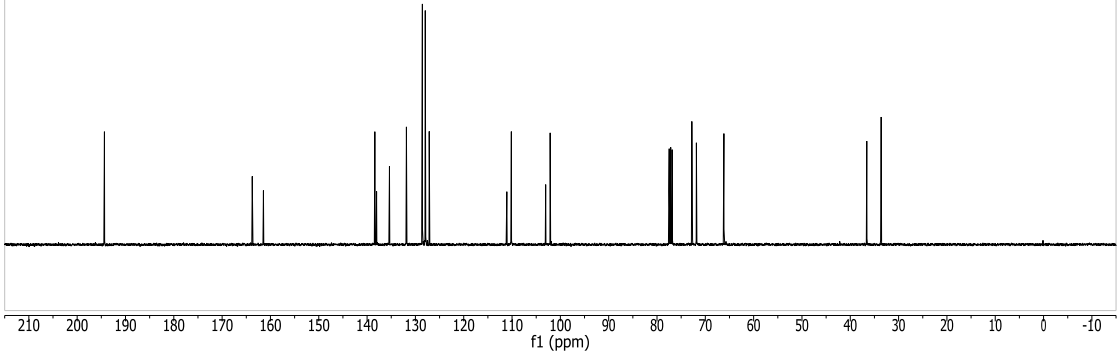


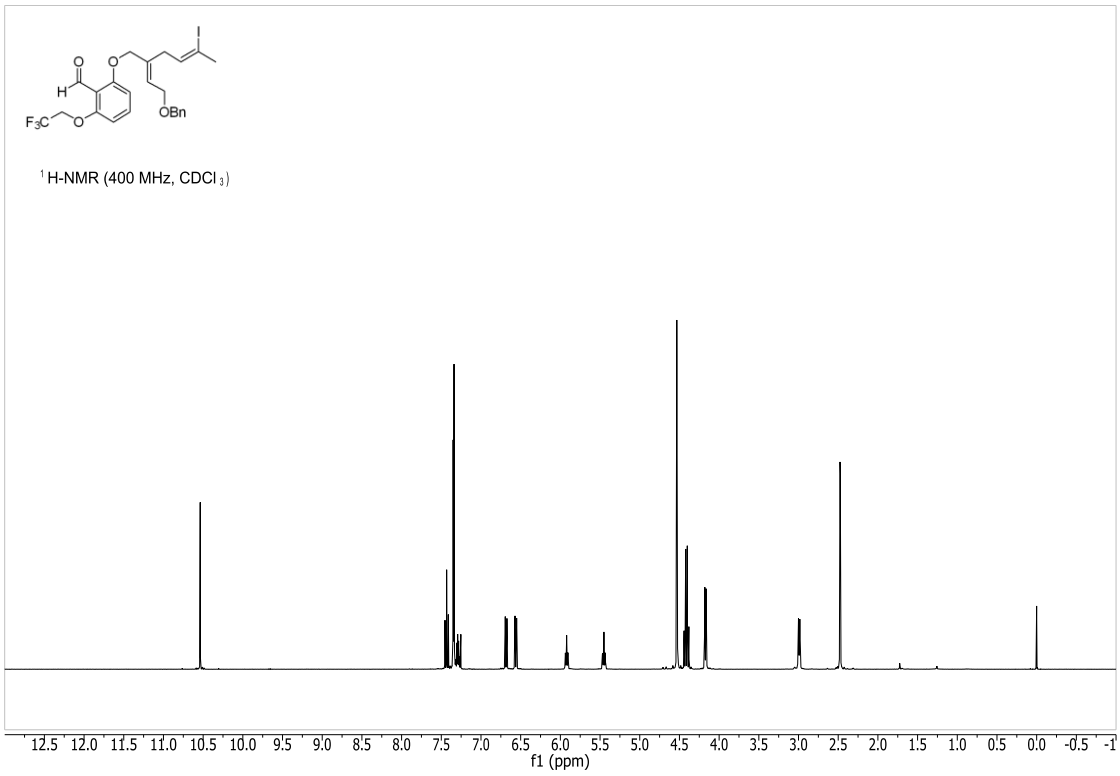
^{1}H-NMR (400 MHz, $CDCl_3$)

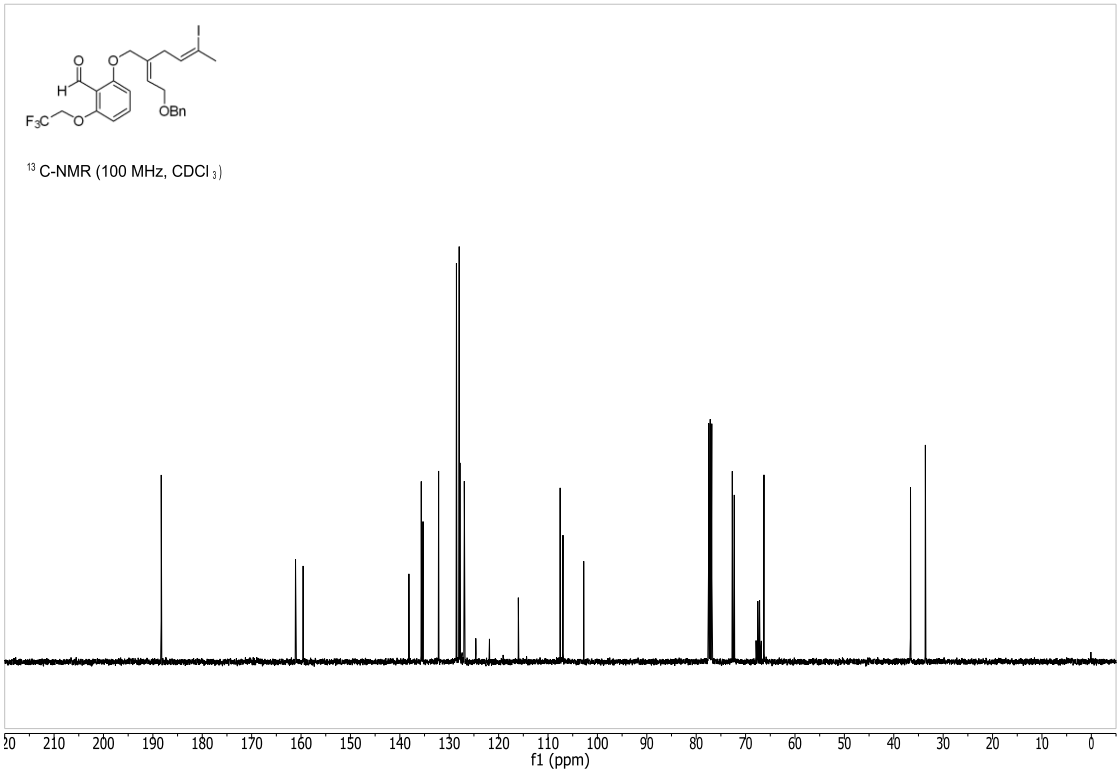


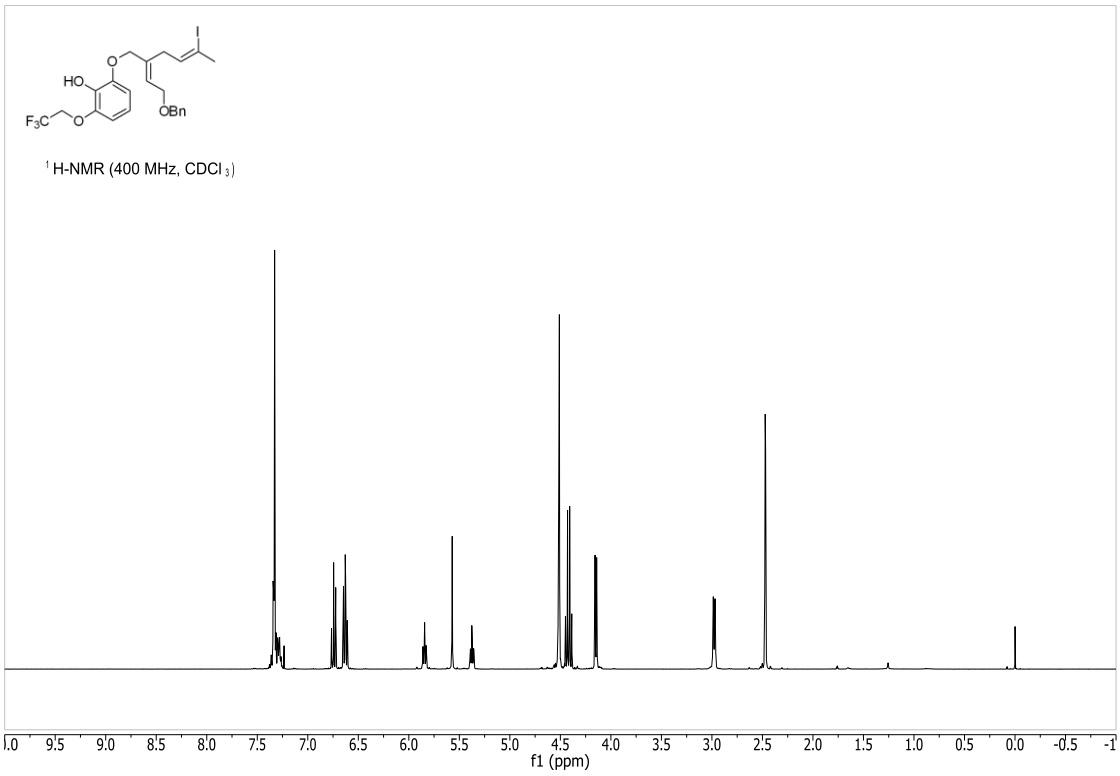


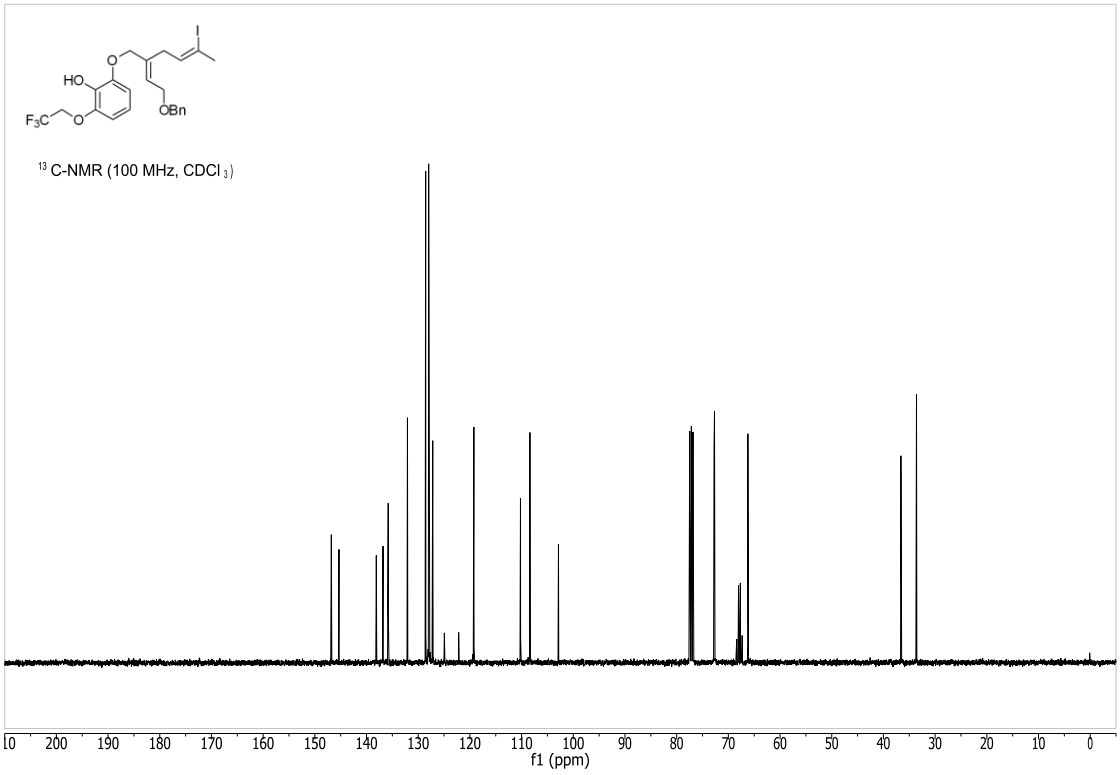
^{13}C-NMR (100 MHz, $CDCl_3$)

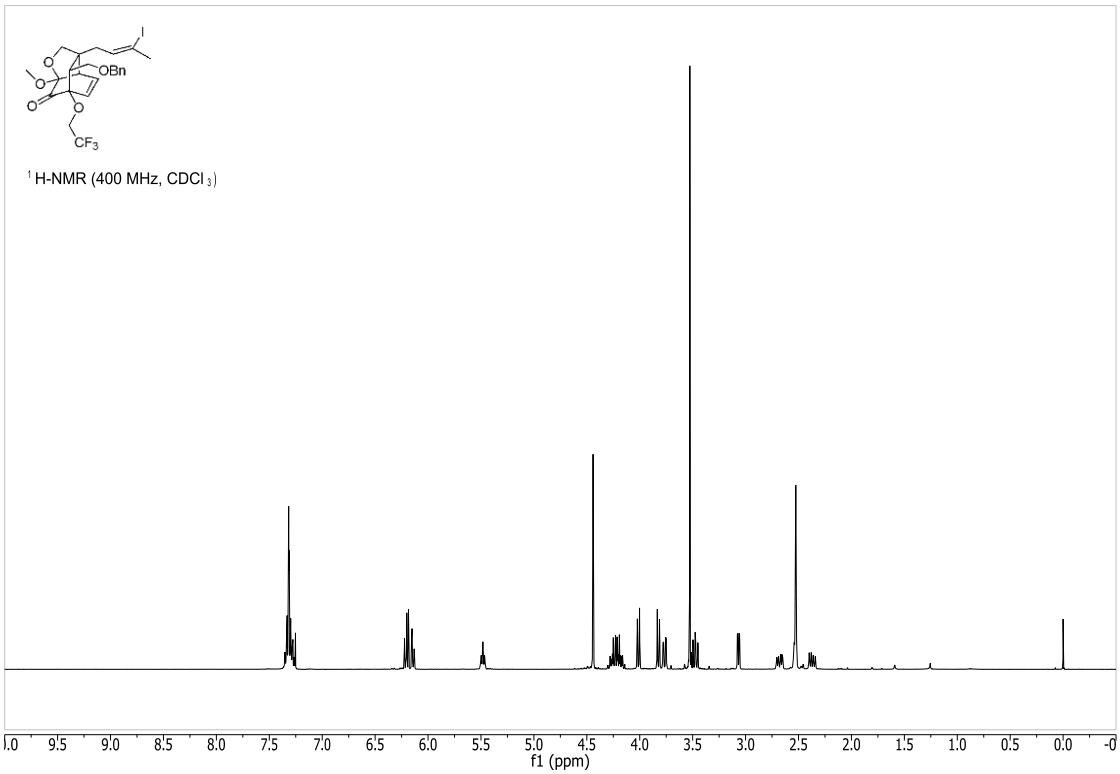


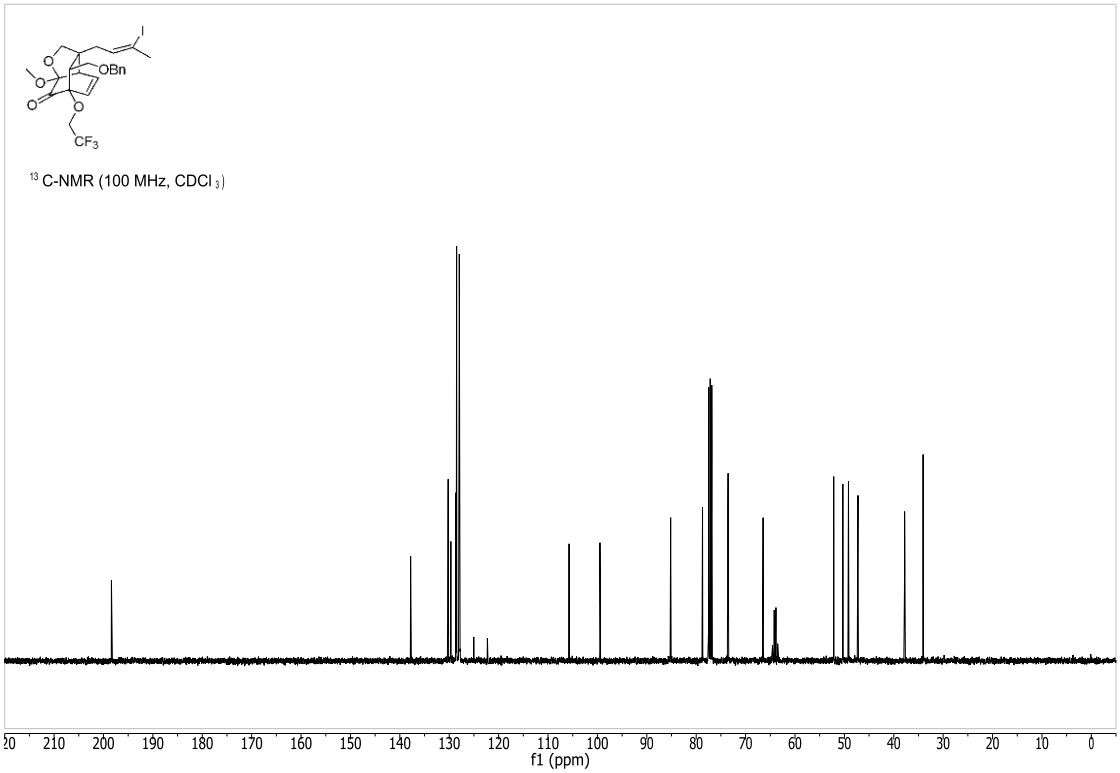

H
O
O
I
OBn
F3C
O
1 H-NMR (400 MHz, CDCl 3)
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)

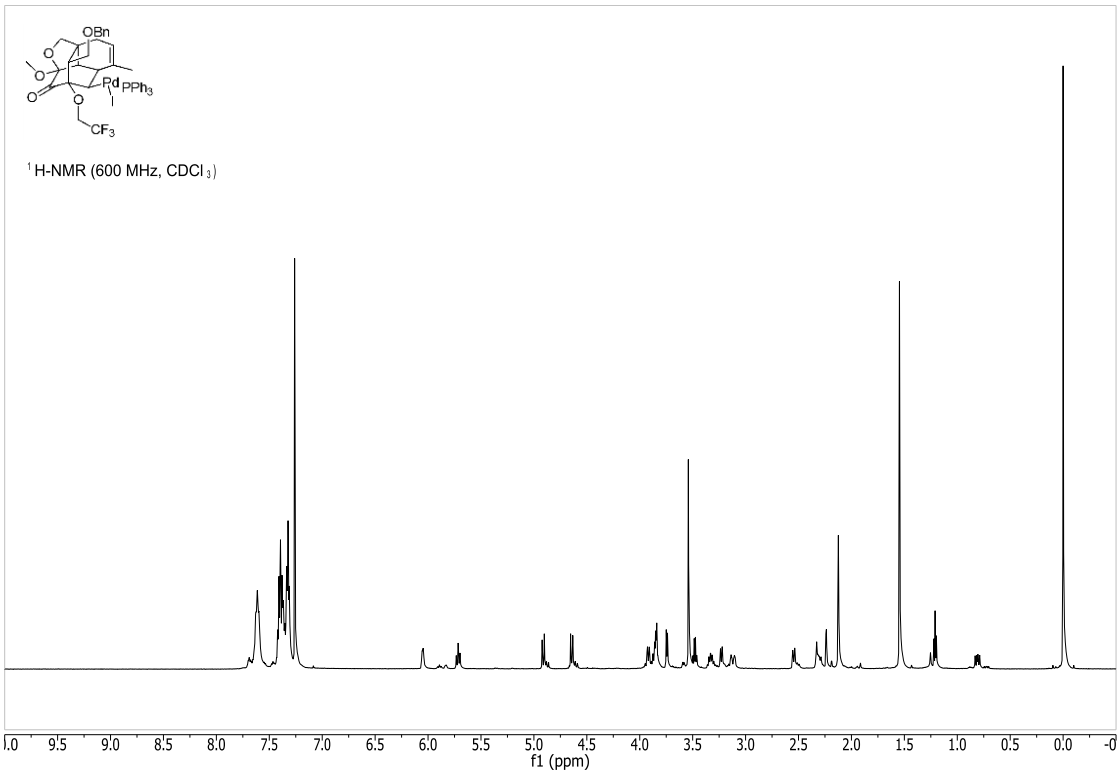

H
O
O
I
OBn
F3C
O
13 C-NMR (100 MHz, CDCl 3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

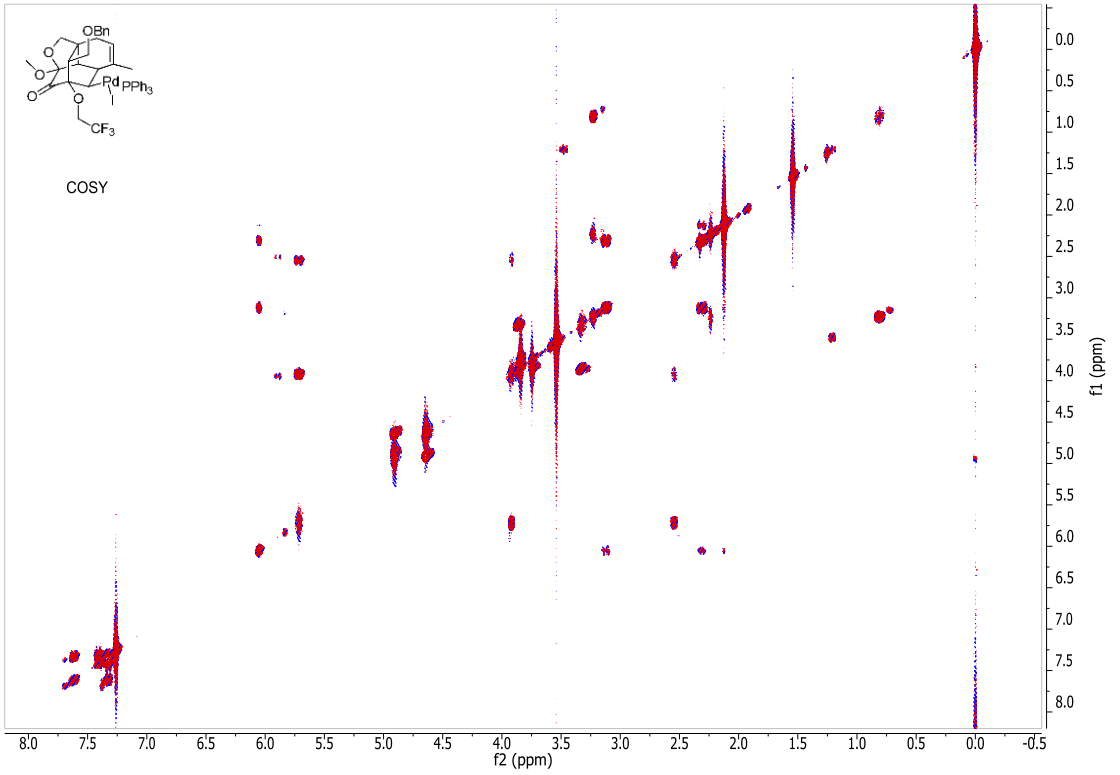

HO
O
I
OBn
F3C
O
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

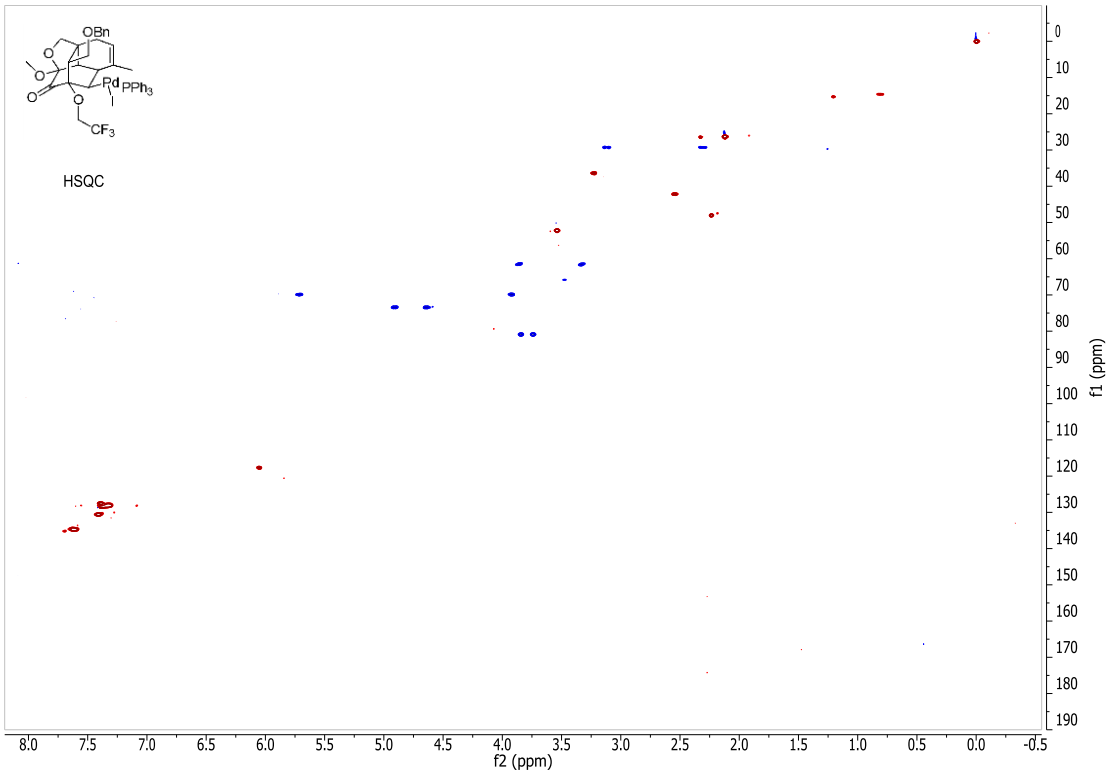

HO
O
I
OBn
F3C
O
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

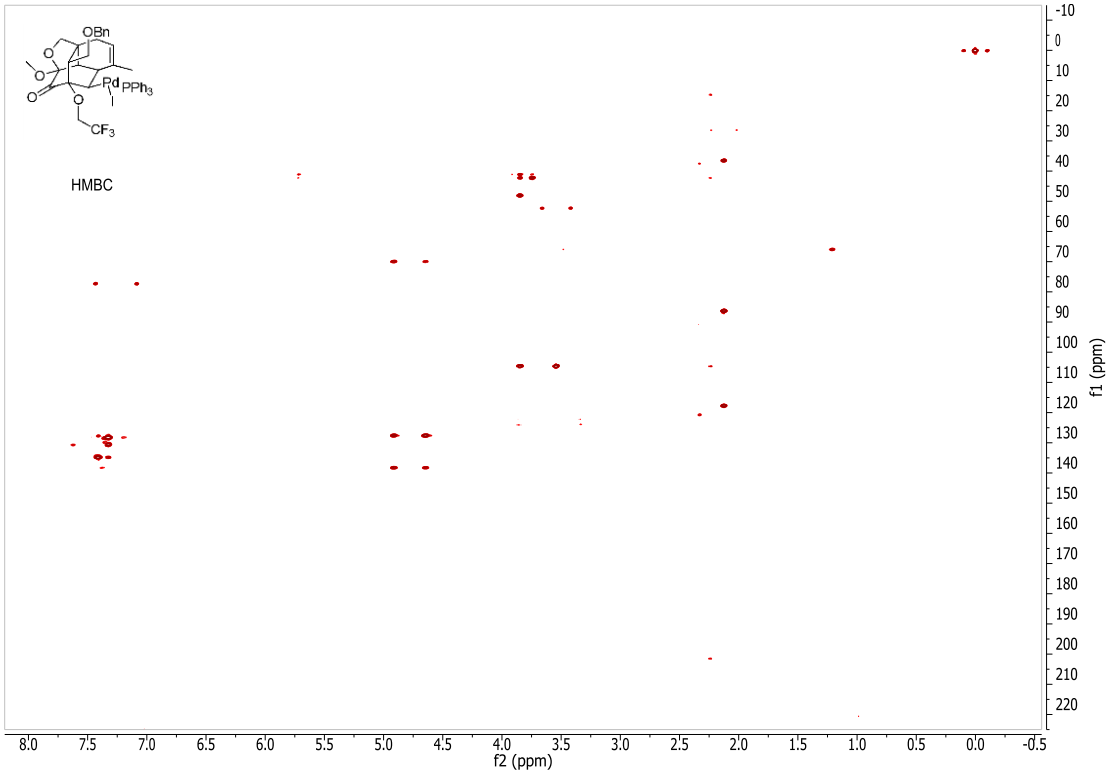

OBn
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

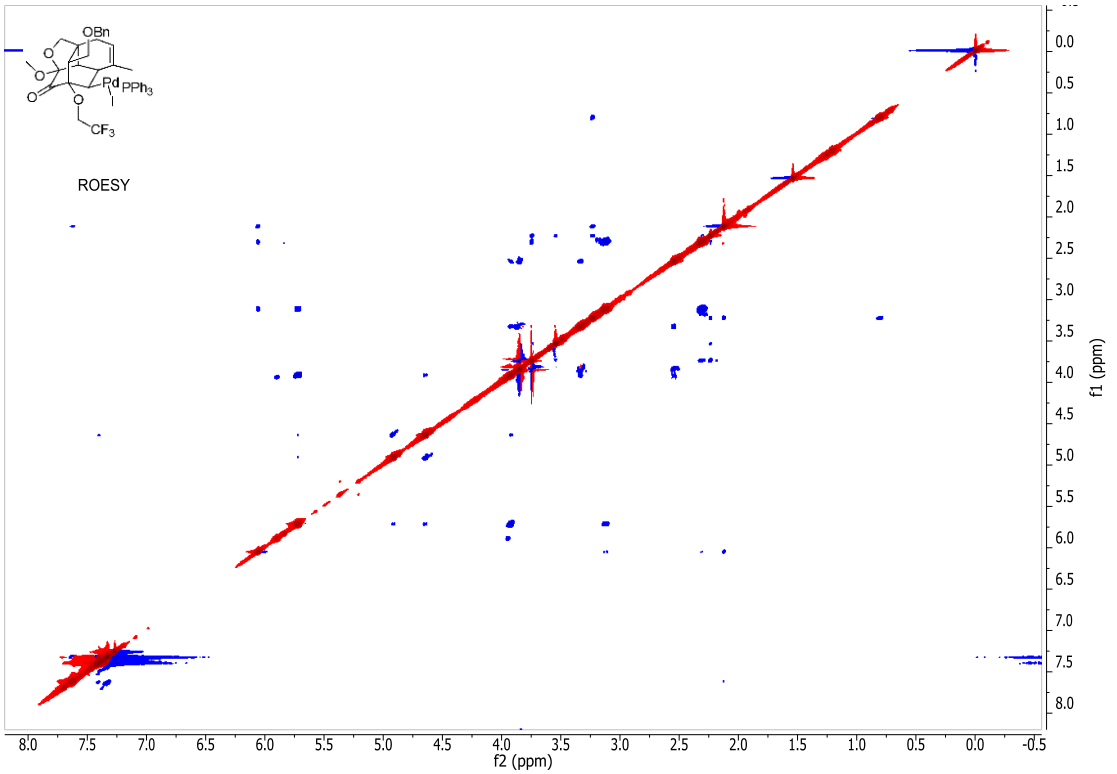

OBn
CF3
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)


OBn
O
O
O
Pd
PPh3
O
CF3
1H-NMR (600 MHz, CDCl3)
f1 (ppm)


OBn
O
O
O
Pd
PPh3
O
CF3
COSY
f2 (ppm)
f1 (ppm)


OBn
Pd
PPh3
CF3
HSQC
f2 (ppm)
f1 (ppm)


OBn
Pd
PPh3
CF3
HMBC
f2 (ppm)
f1 (ppm)


OBn
Pd
PPh3
CF3
ROESY
f2 (ppm)
f1 (ppm)

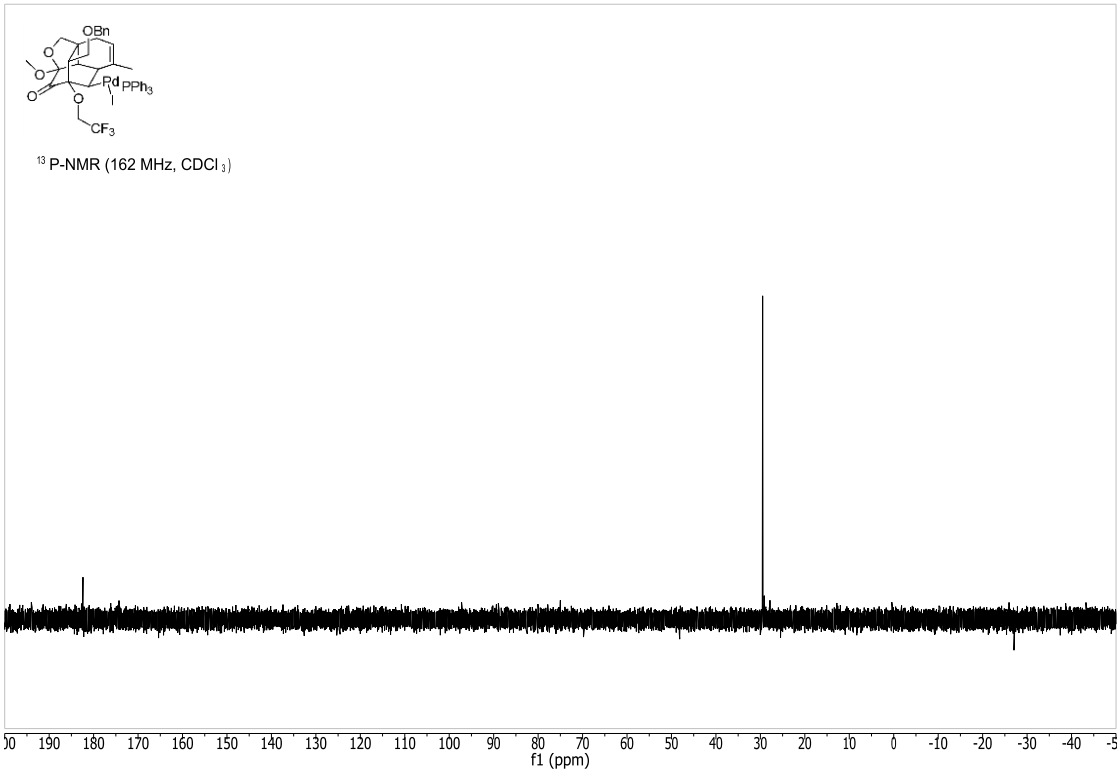
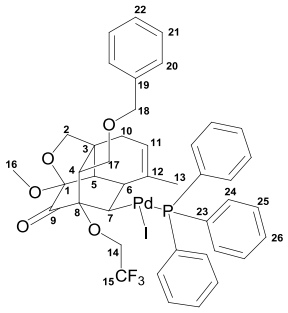
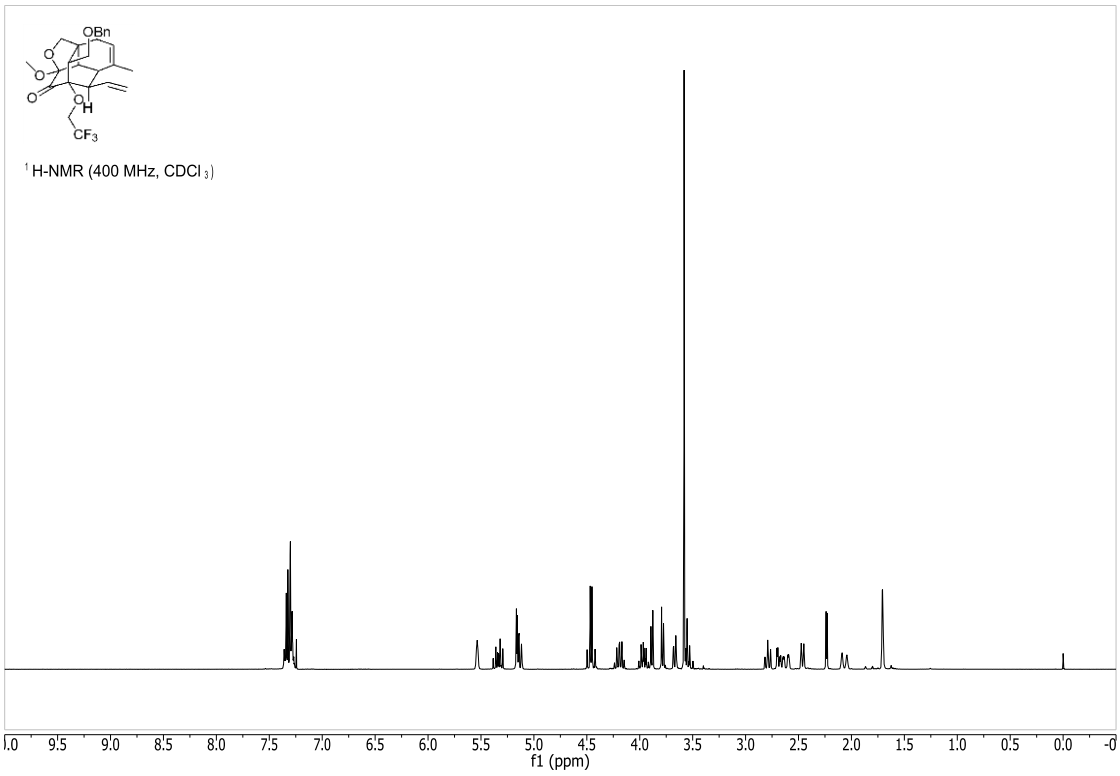

OBn
Pd
PPh3
CF3
13 P-NMR (162 MHz, CDCl 3)
f1 (ppm)

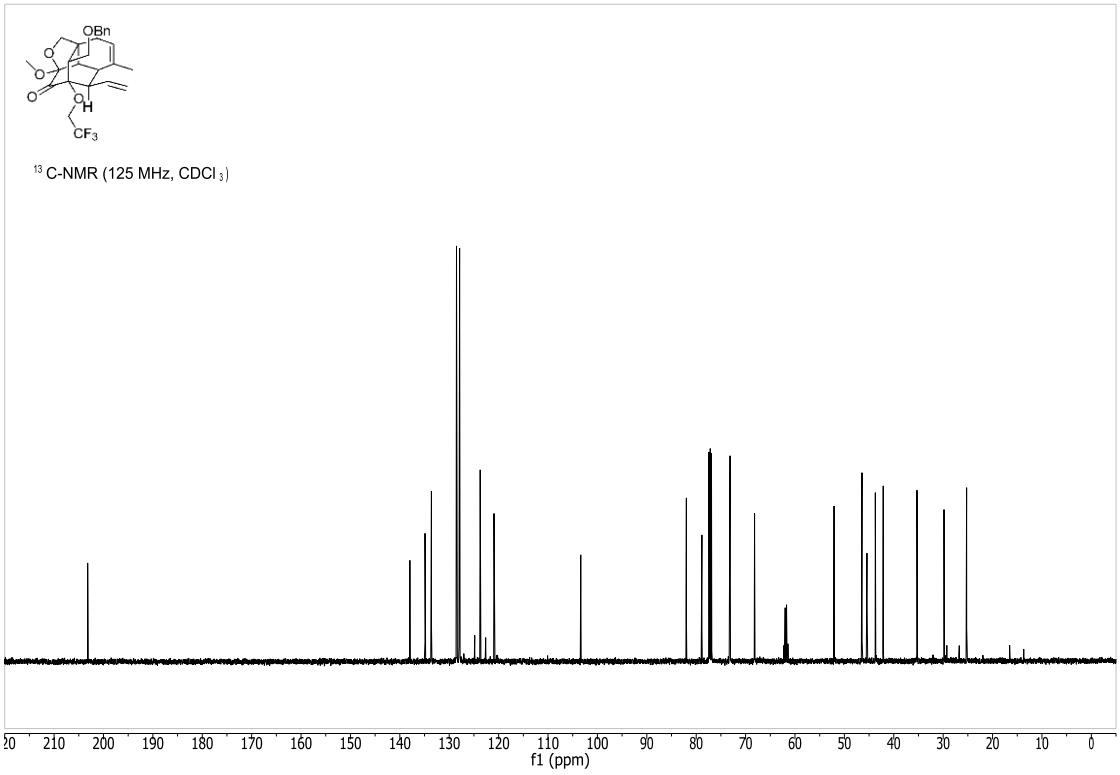
Table A2.1. 2D-NMR Data of Compound **3.17**

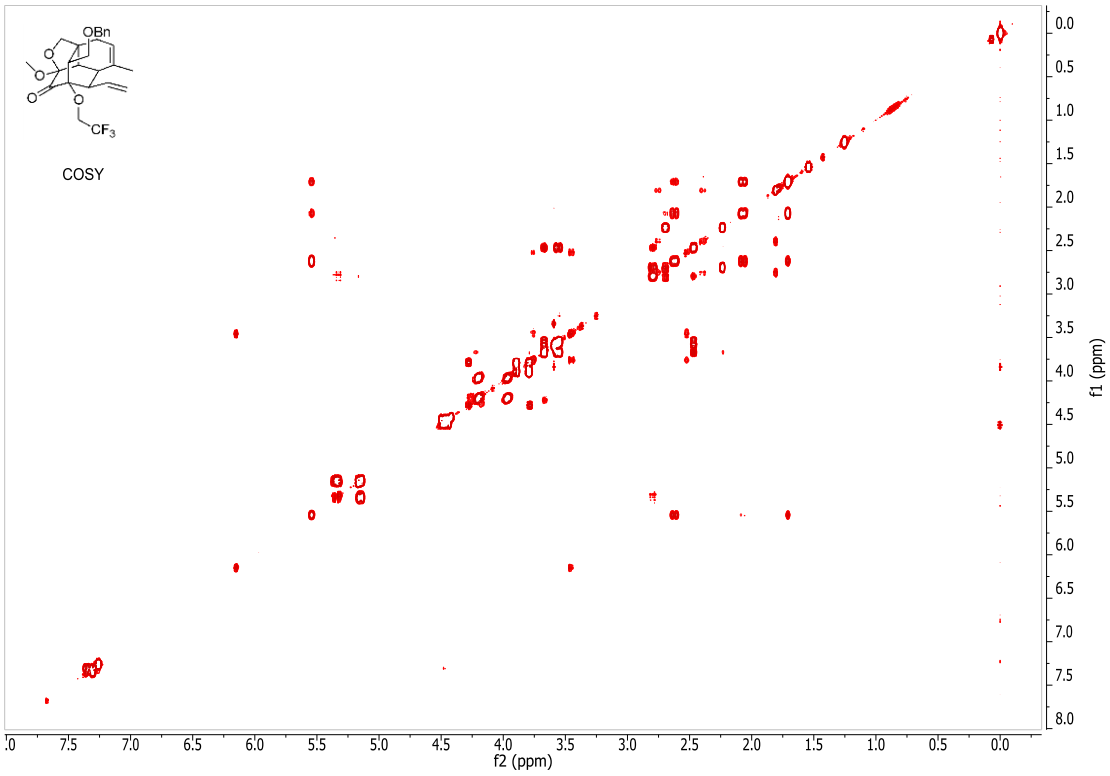


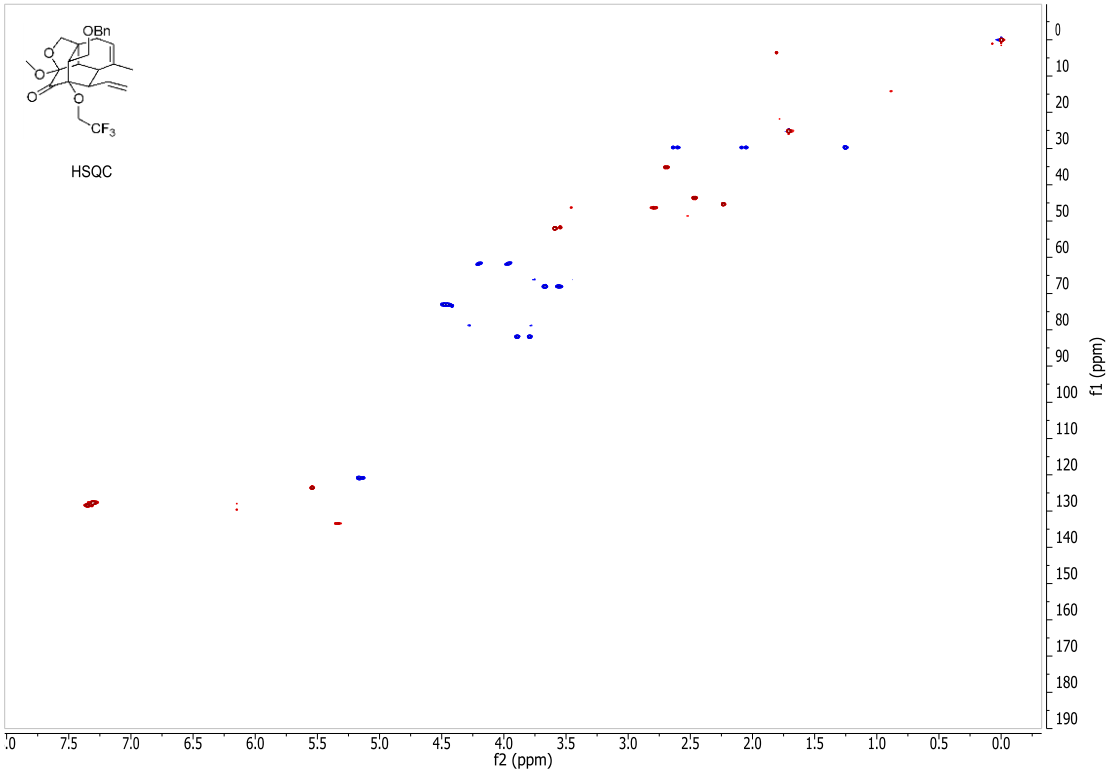
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	ROESY correlations
1	104.5		Cq			
2a	80.9	3.84	CH_2	H-2b	C-1, C-3, C-4, C-5	H-4
2b		3.74	CH_2	H-2a	C-3, C-4	H-5, H-10b
3	41.0		Cq			
4	42.2	2.55	CH	H-17a		H-2a, H-14b, H-17b
5	48.0	2.24	CH	H-6	C-1, C-4, C-7, C-9	H-2b, H-6
6	36.4	3.23	CH	H-5, H-7		H-5, H-13
7	14.6	0.81	CH	H-4, H-6		H-6
8	122.1		Cq			
9	201.4		Cq			
10a	29.3	3.12	CH_2	H-10b, H-11		H-10b, H-11
10b		2.31	CH_2	H-10a, H-11, H-13		H-10a
11	117.7	6.05	CH	H-10a, H-10b, H-13		H-10a, H-10b, H-13
12	86.3		Cq			
13	26.3	2.12	CH_3	H-11	C-6, C-11, C-12	H-6, H-11
14a	61.5	3.86	CH_2	H-14b	C-8, C-15	H-14b
14b		3.33	CH_2	H-14a	C-8, C-15	H-4, H-14a
15	123.9		Cq			
16	52.2	3.54	CH_3		C-1	H-5
17a	69.9	5.72	CH_2	H-4, H-17b	C-3, C-4	H-10a, H-17b
17b		3.92	CH_2	H-17a		H-4, H-11, H-14b, H-18b
18a	73.4	4.91	CH_2	H-18b	C-17, C-19, C-20	H-17a, H-18b
18b		4.64	CH_2	H-18a	C-17, C-19, C-20	H-17a, H-17b, H-18a
19	138.1		Cq			
20	127.5	7.39	CH		C-19	H-18b
21	128.5	7.37	CH			
22	128.3	7.36	CH			

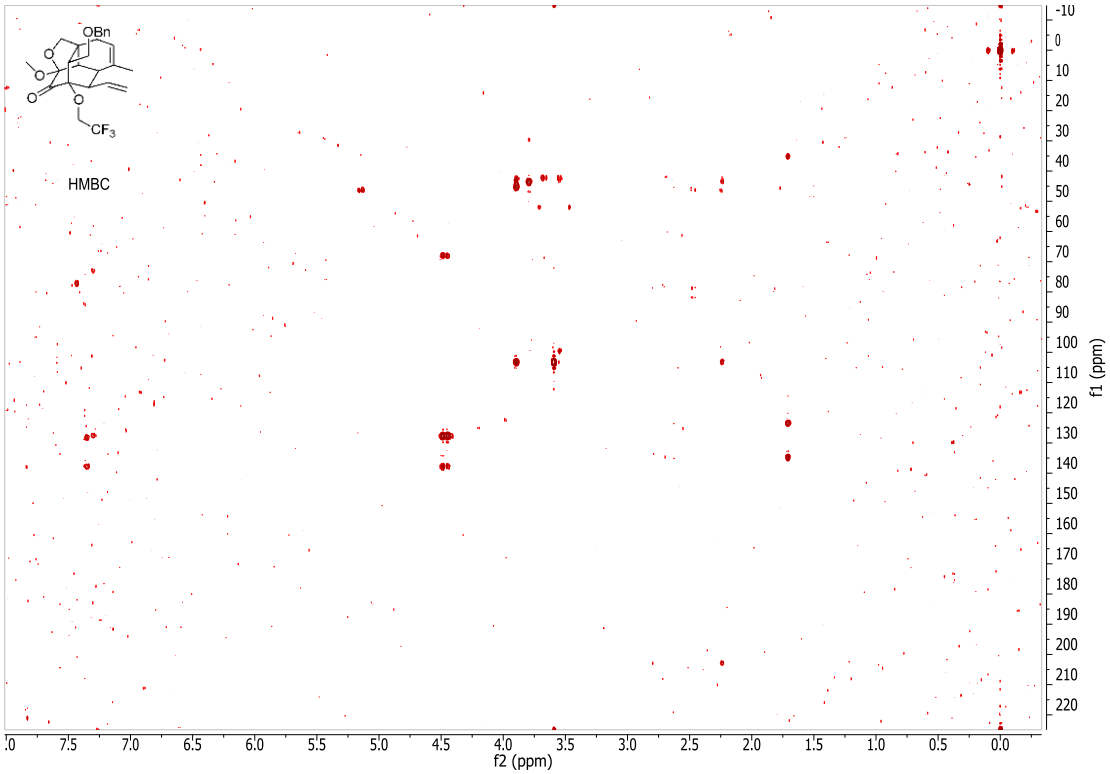
23	129.7		Cq			
23	128.2	7.32	CH	H-25, H-26	C-25, C-26	H-13
25	134.8	7.61	CH	H-24, H-26	C-26	H-7, H-13, H-17a, H-17b
26	130.6	7.41	CH	H-24, H-25	C-25	


OBn
O
O
O
H
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)


OBn
O
O
O
H
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


OBn
CF3
COSY
f1 (ppm)
f2 (ppm)


OBn
CF3
HSQC
f1 (ppm)
f2 (ppm)


OBn
O
O
O
O
CF3
HMBC
f2 (ppm)
f1 (ppm)

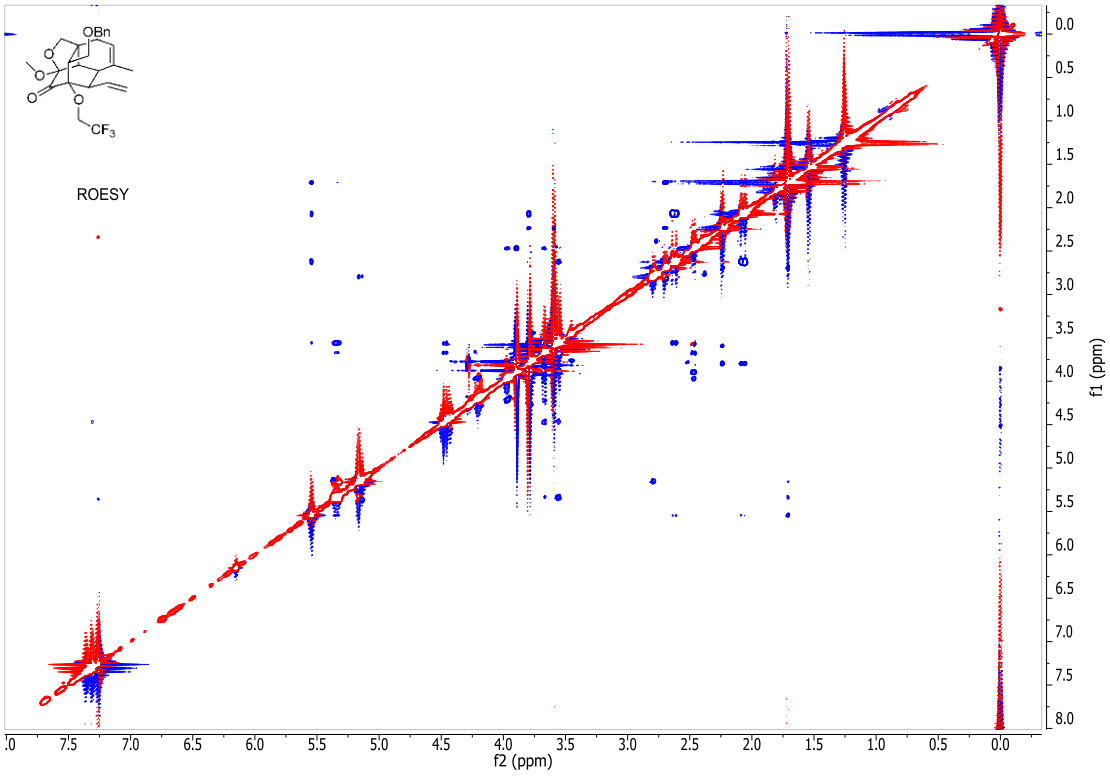
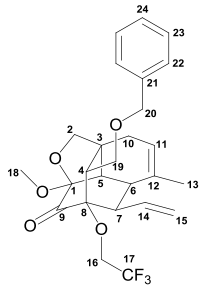
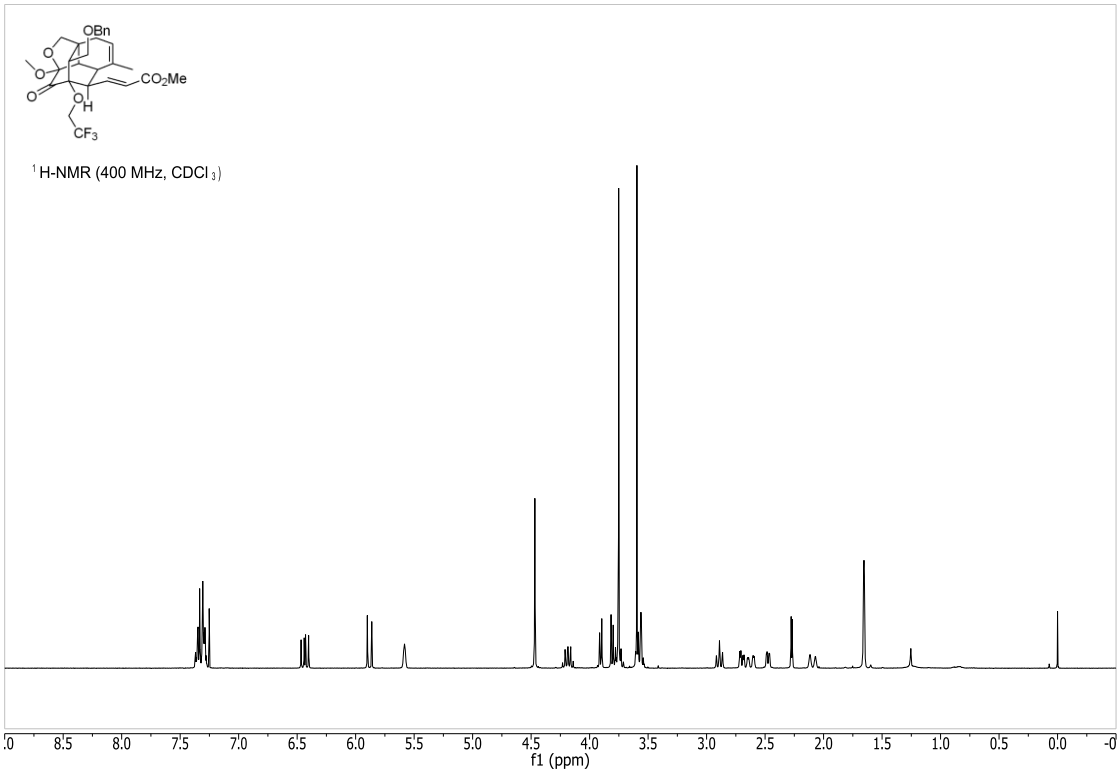
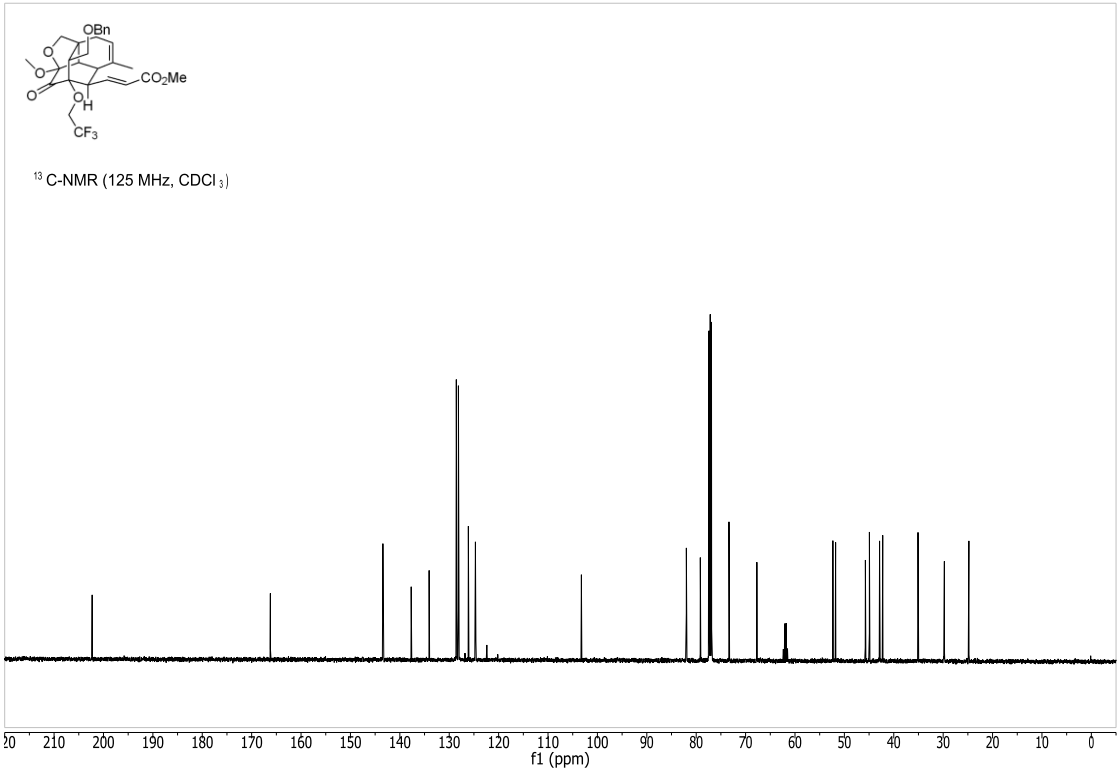

OBn
O
O
O
O
CF3
ROESY
f2 (ppm)
f1 (ppm)

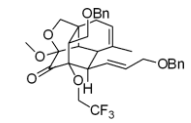
Table A2.2. 2D-NMR Data of Compound **3.18**



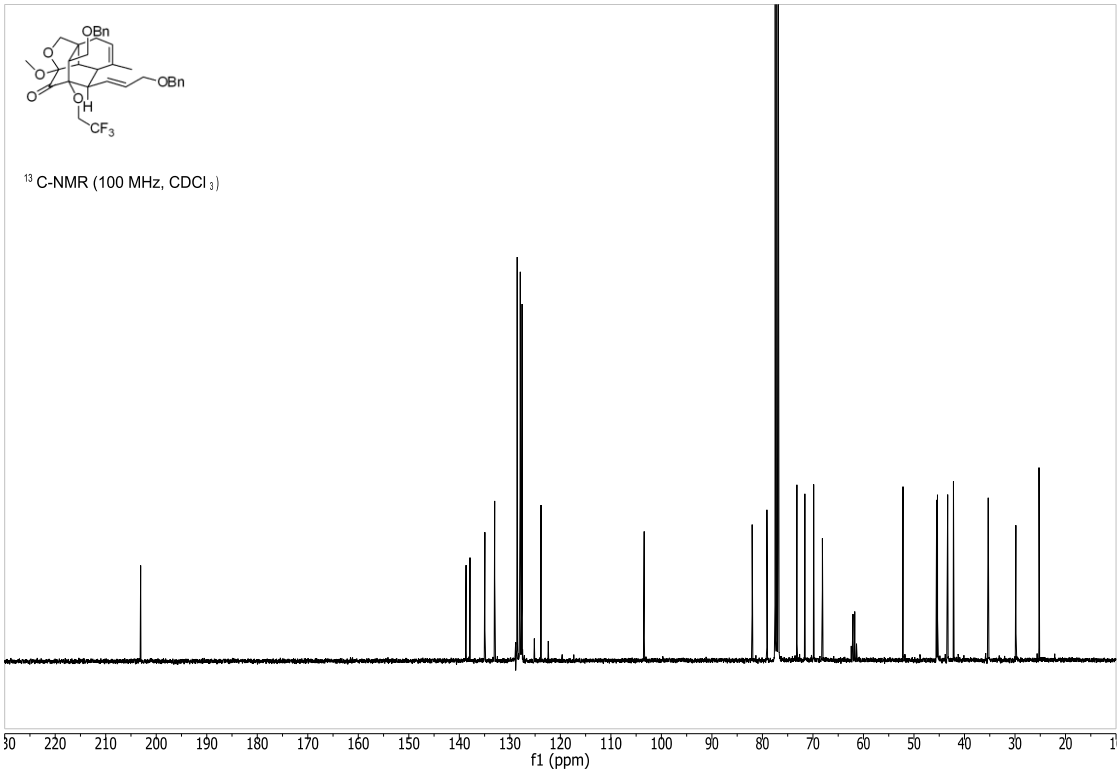
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	ROESY correlations
1	103.4		Cq			
2a	82.0	3.90	CH_2	H-2b	C-1, C-4, C-5	H-4
2b		3.79	CH_2	H-2a	C-3, C-4	H-5, H-10b
3	42.1		Cq			
4	43.7	2.47	CH	H-7, H-19a, H-19b		H-2a, H-16b, H-19a
5	45.4	2.25	CH	H-6	C-3, C-4	H-2b, H-6, H-18
6	35.3	2.70	CH	H-5, H-7		H-5, H-13
7	46.4	2.80	CH	H-4, H-6, H-14		H-15a
8	78.8		Cq			
9	203.2		Cq			
10a	29.8	2.62	CH_2	H-10b, H-11, H-13		H-10b, H-19b
10b		2.07	CH_2	H-10a, H-13		H-2b, H-10a
11	123.7	5.55	CH	H-10a, H-13		H-10a, H-10b, H-13
12	134.9		Cq			
13	25.2	1.71	CH_3	H-10a, H-10b, H-11	C-6, C-11, C-12	H-6, H-11, H-14
14	133.6	5.34	CH	H-7, H-15a, H-15b		H-19b
15a	120.9	5.17	CH_2	H-14, H-15b		H-7
15b		5.15	CH_2	H-14, H-15a	C-7	
16a	61.7	4.20	CH_2	H-16b		
16b		3.97	CH_2	H-16a		H-4
17	123.7		Cq			
18	52.0	3.59	CH_3		C-1	
19a	68.2	3.67	CH_2	H-4, H-19b	C-3	H-4, H-20b
19b		3.56	CH_2	H-4, H-19a	C-4, C-8	H-10a, H-14, H-2a
20a	73.1	4.48	CH_2	H-20b, H-23	C-19, C-21, C-22	H-19a
20b		4.46	CH_2	H-20a, H-23	C-19, C-21, C-22	H-19b
21	138.0		Cq			
22	127.9	7.30	CH	H-20b, H-23	C-23	
23	128.5	7.35	CH	H-22, H-24	C-21, C-24	
24	127.9	7.31	CH	H-23		

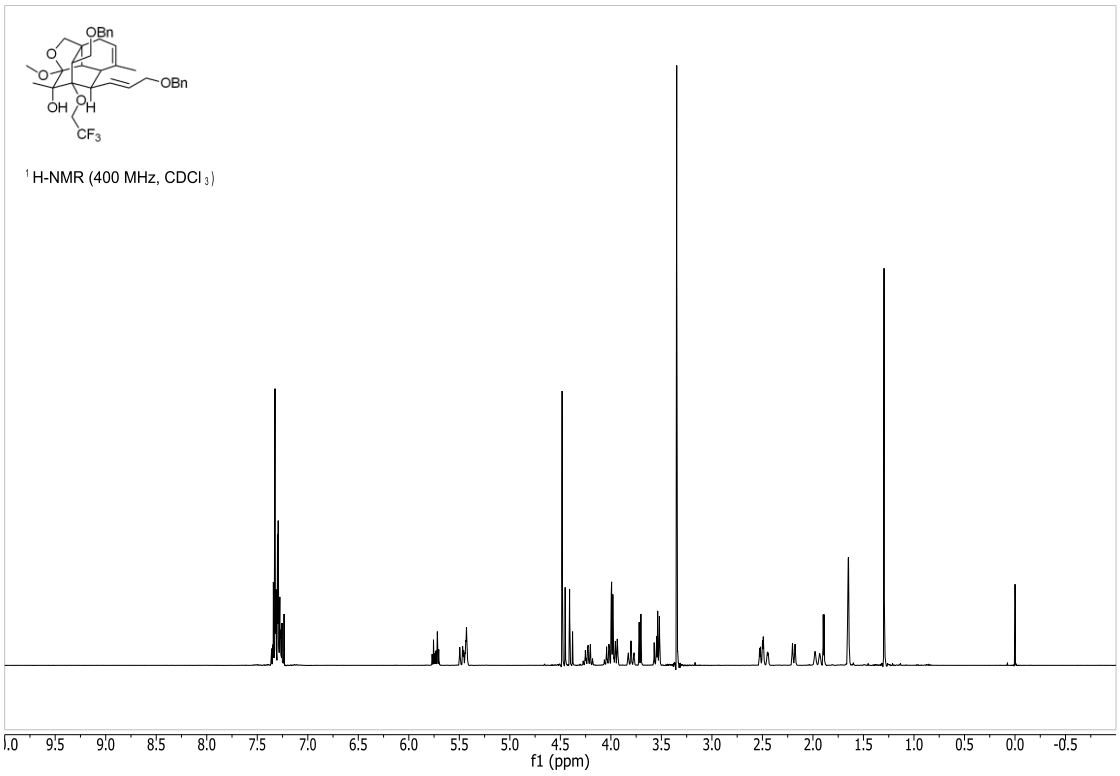

OBn
O
O
O
CO2Me
O
H
CF3
1 H-NMR (400 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

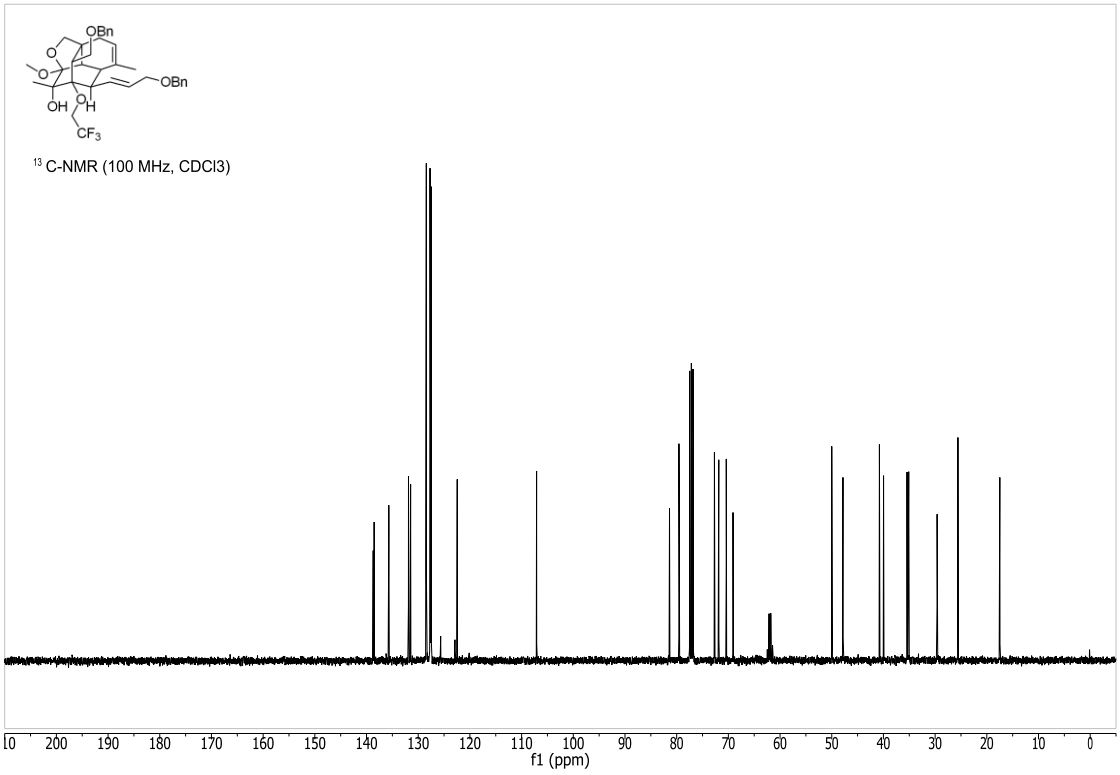

OBn
O
O
O
CO2Me
O
H
CF3
13 C-NMR (125 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

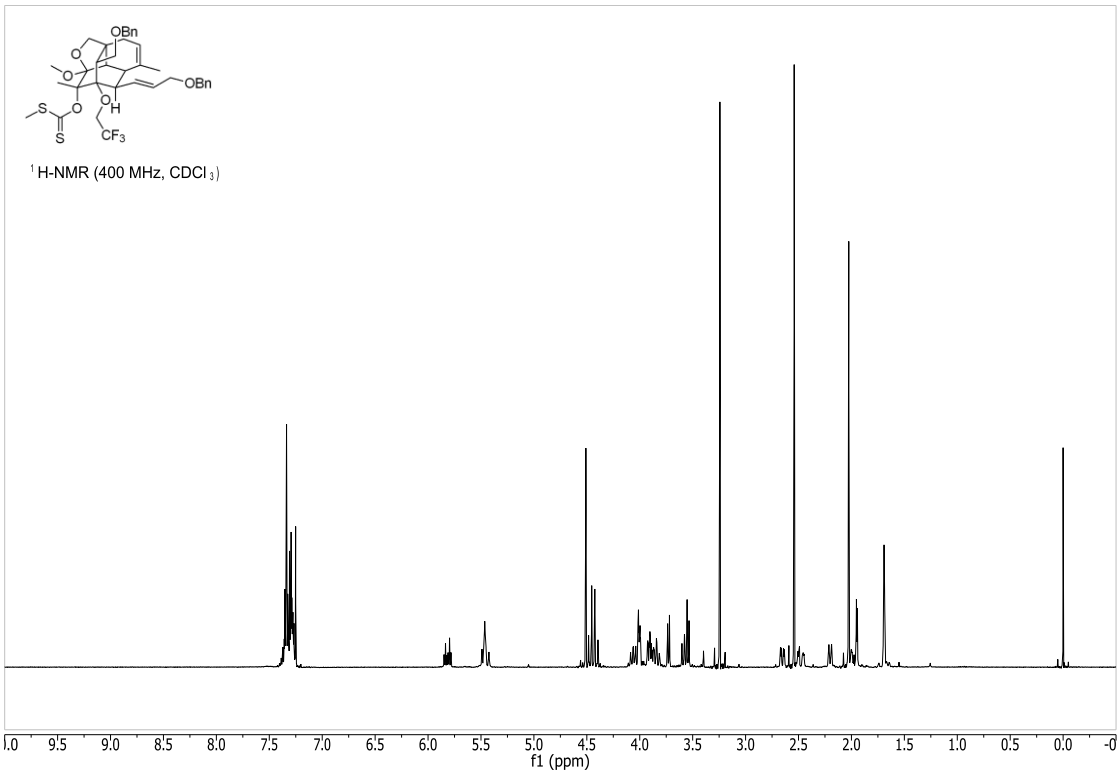


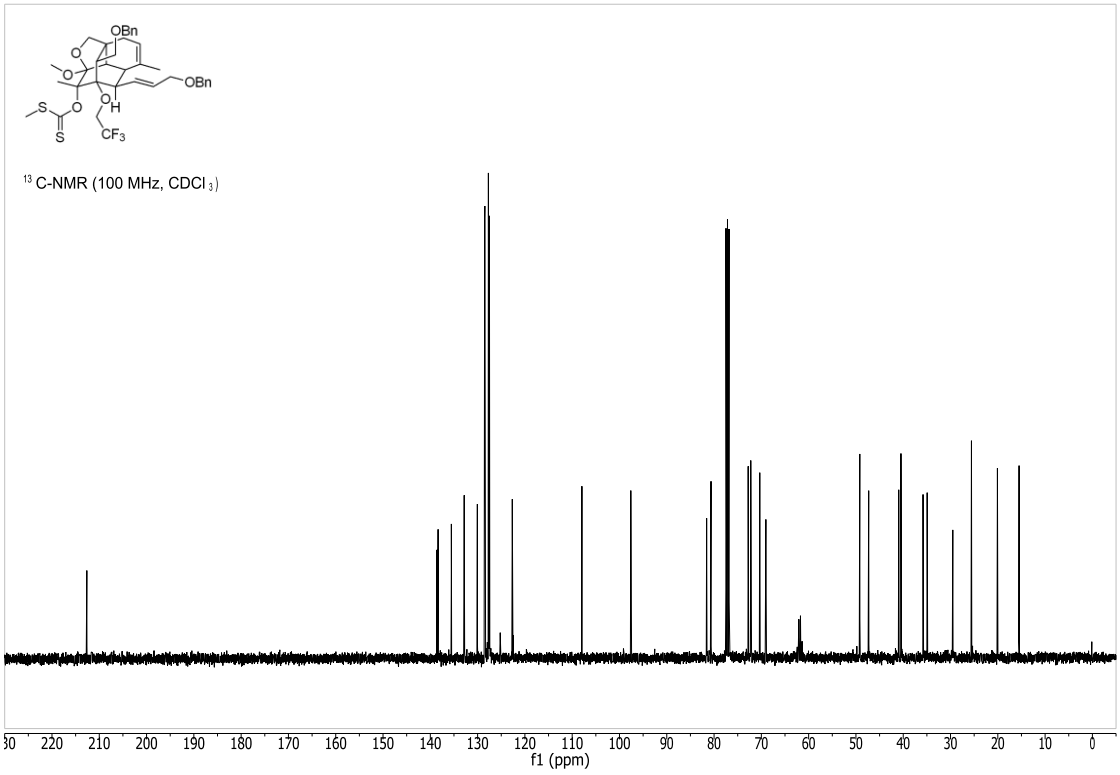
^{1}H-NMR (400 MHz, $CDCl_3$)

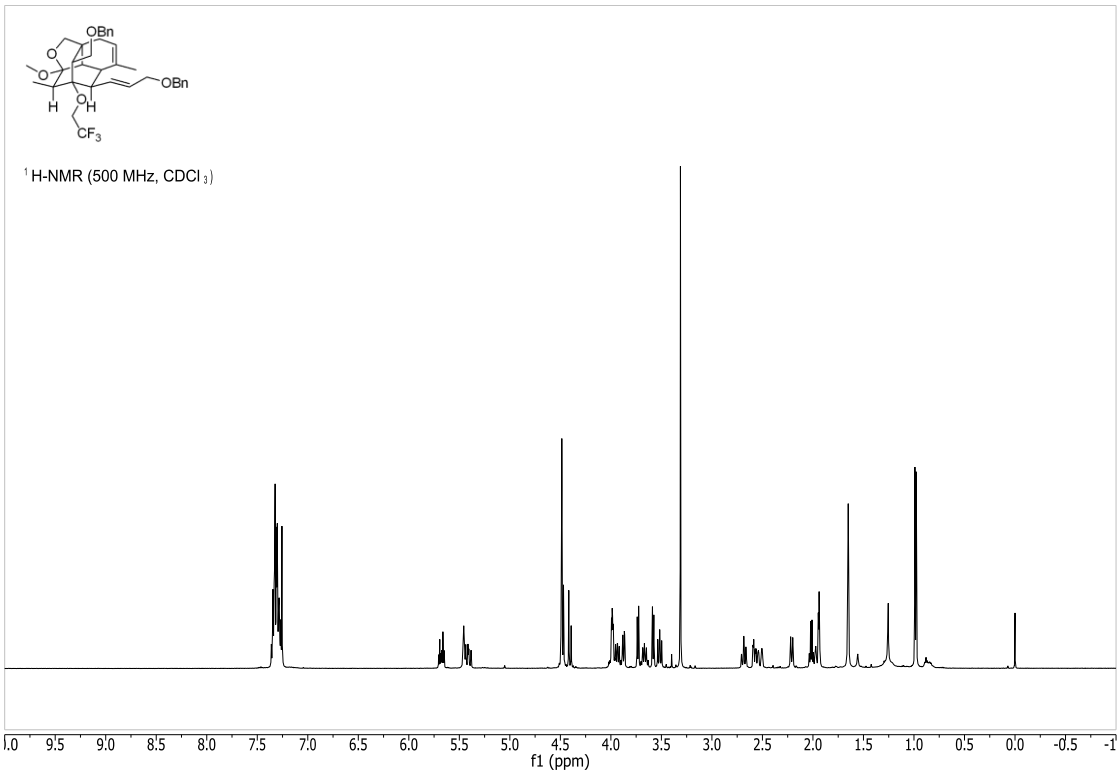


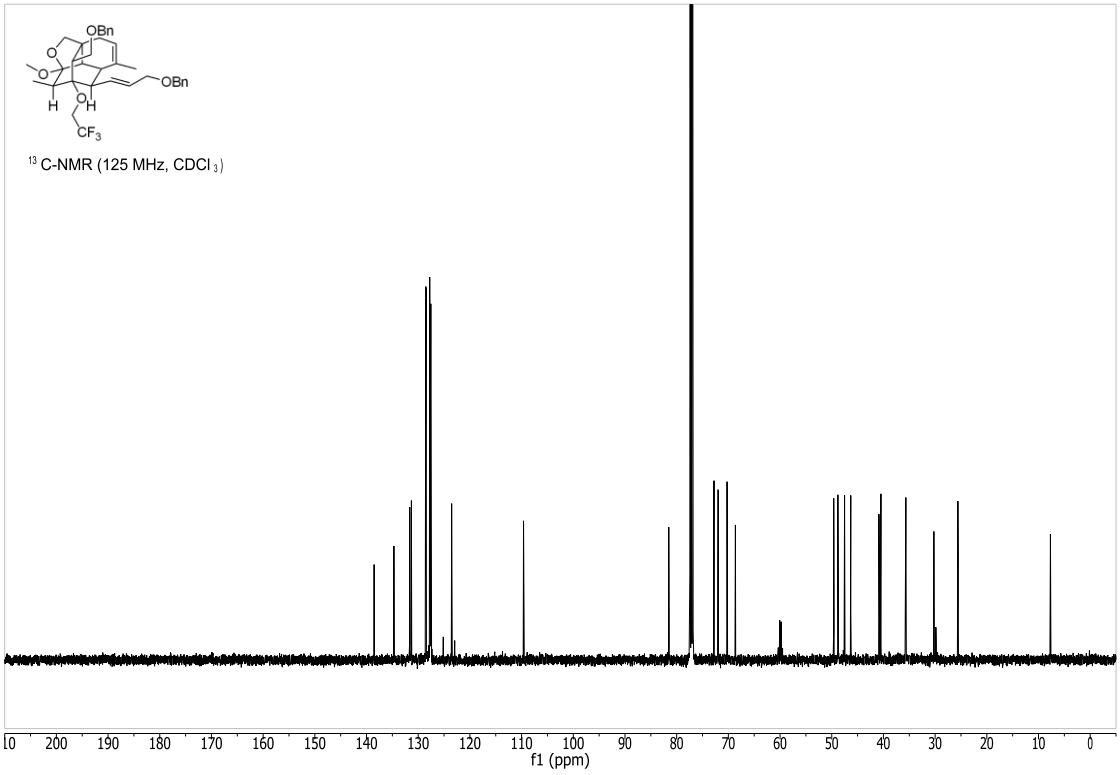

OBn
O
O
OBn
OH
O
H
CF3
1 H-NMR (400 MHz, CDCl 3)
10 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

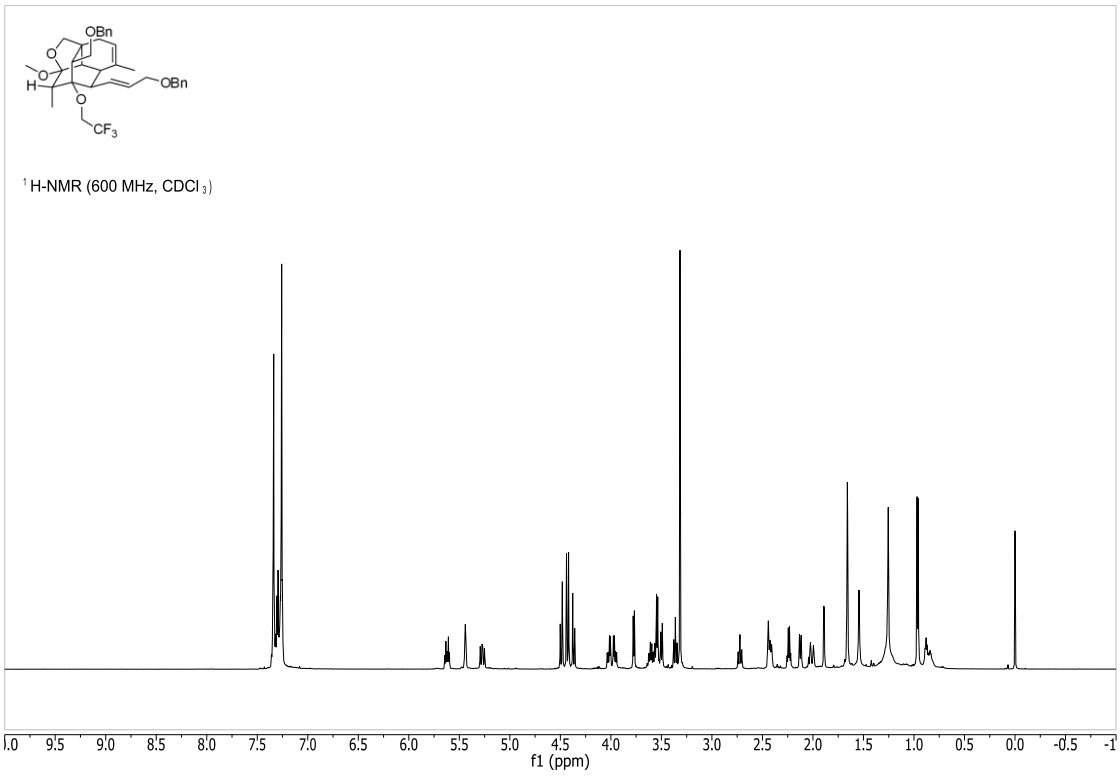

OBn
O
O
OBn
OH
O
H
CF3
13 C-NMR (100 MHz, CDCl3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

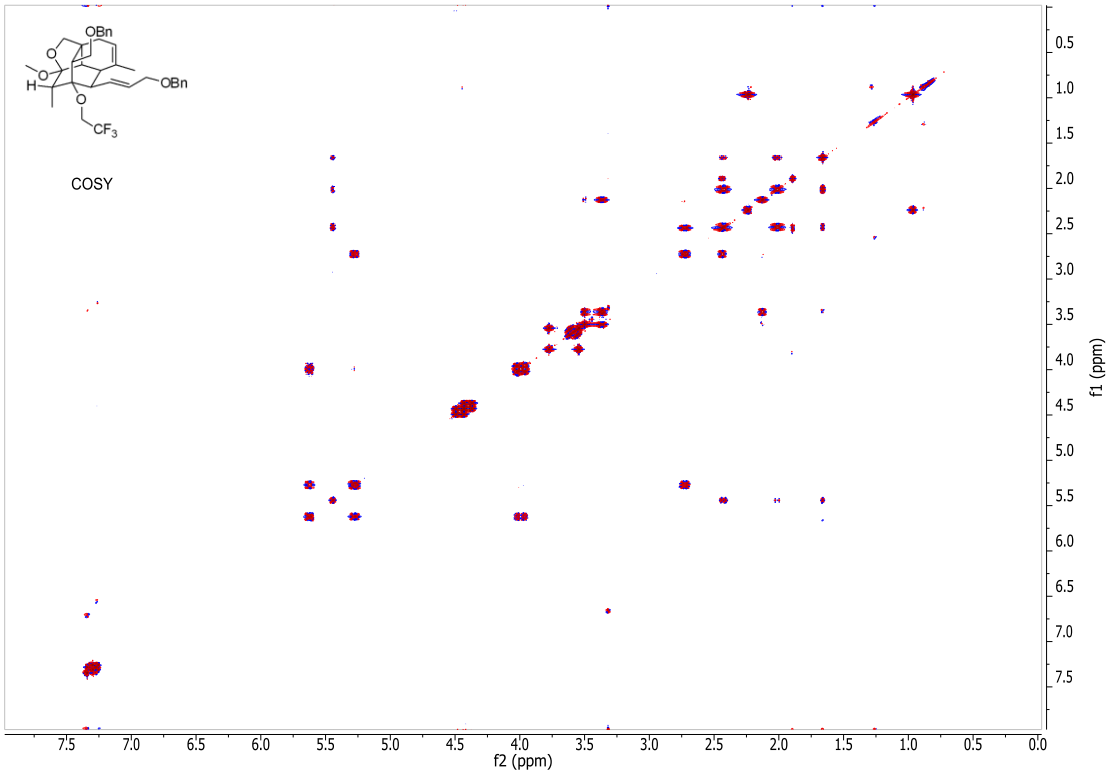

OBn
OBn
O
O
O
H
S
S
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

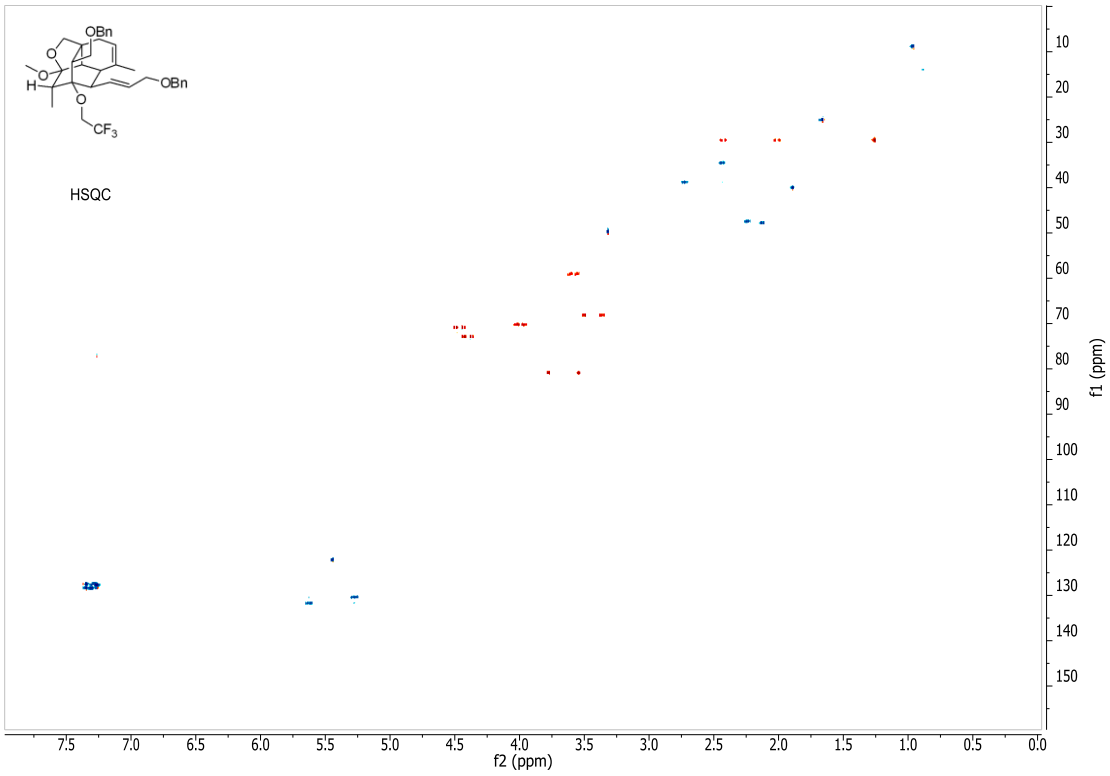

OBn
OBn
O
O
O
H
S
S
CF3
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

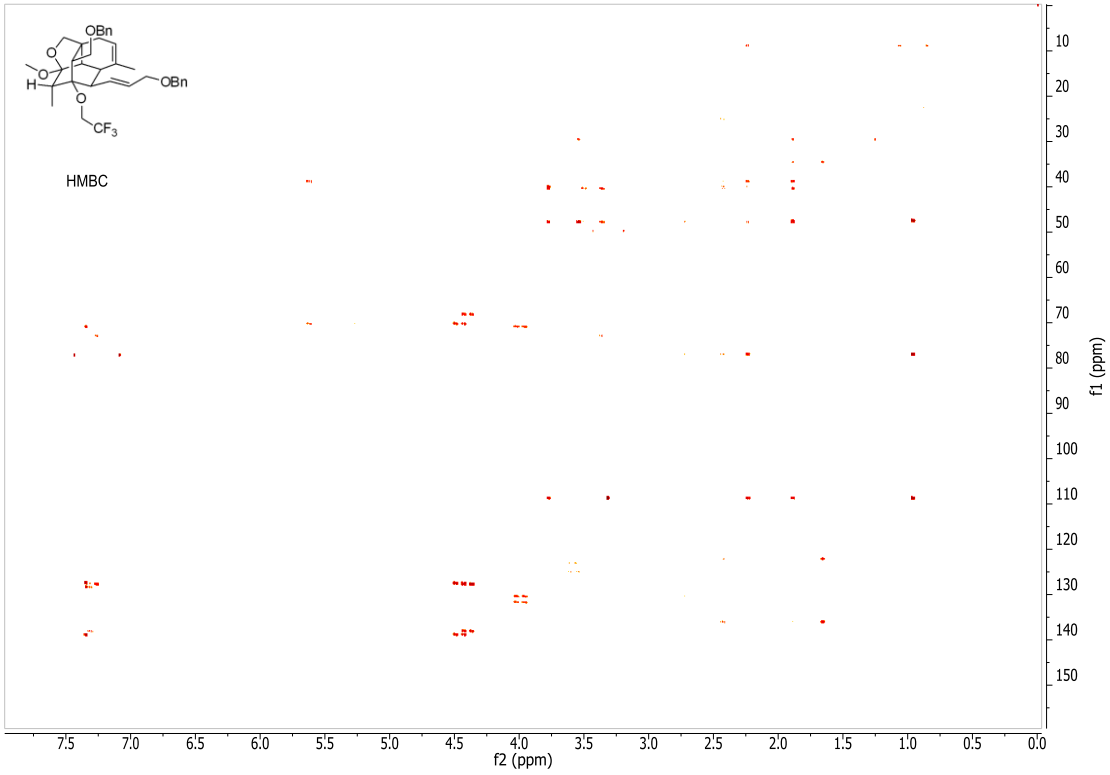

OBn
OBn
O
O
H
O
H
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)


OBn
OBn
O
O
H
O
H
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


OBn
O
H
O
OBn
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)


OBn
O
H
O
OBn
O
CF3
COSY
f2 (ppm)
f1 (ppm)


OBn
OBn
H
O
O
CF3
HSQC
f1 (ppm)
f2 (ppm)


OBn
OBn
H
O
O
CF3
HMBC
f1 (ppm)
f2 (ppm)

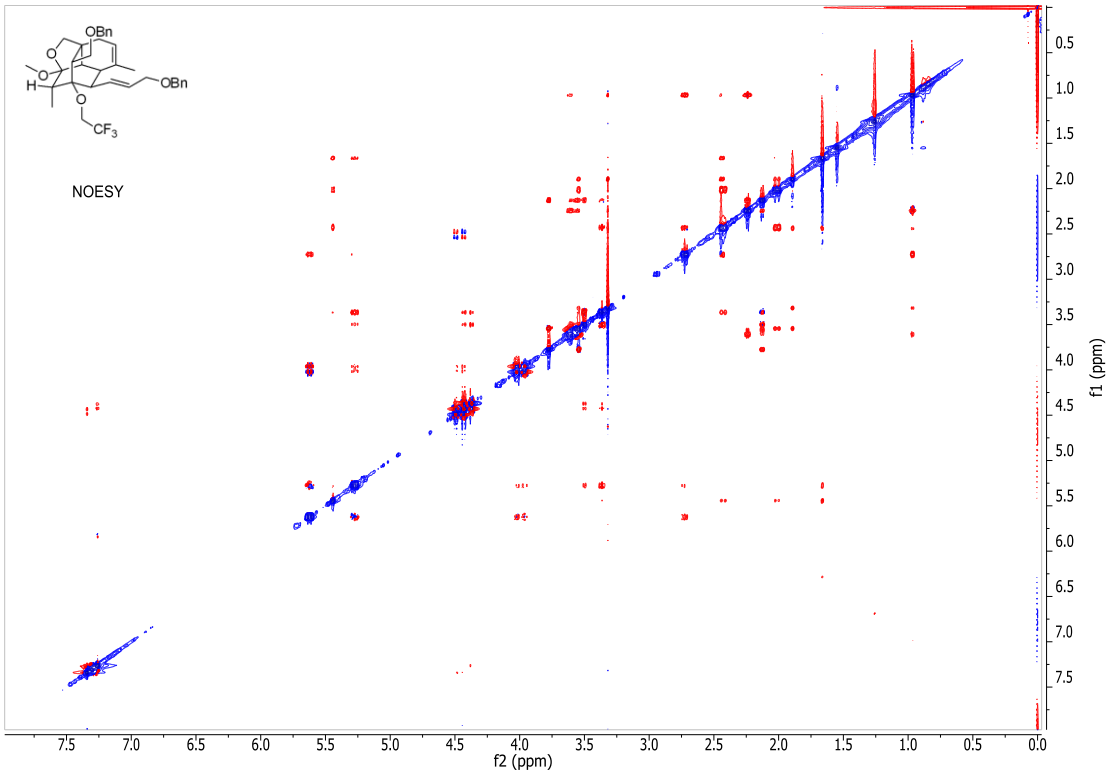
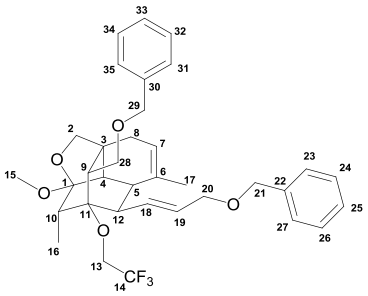
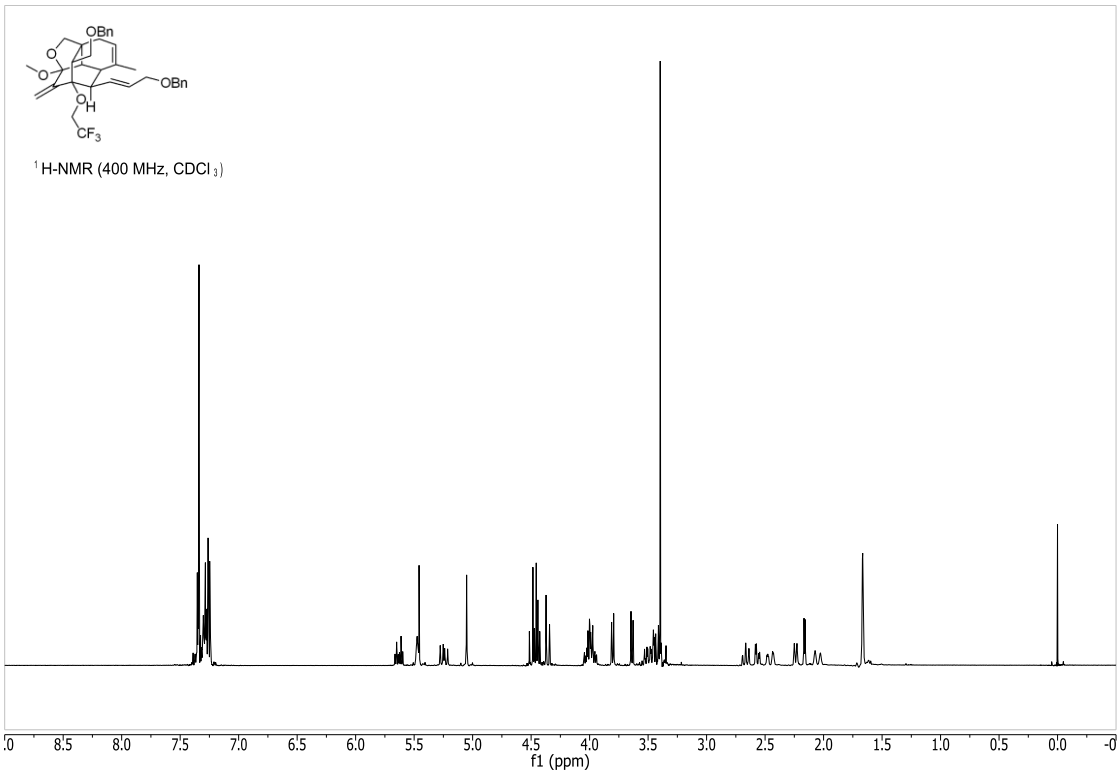


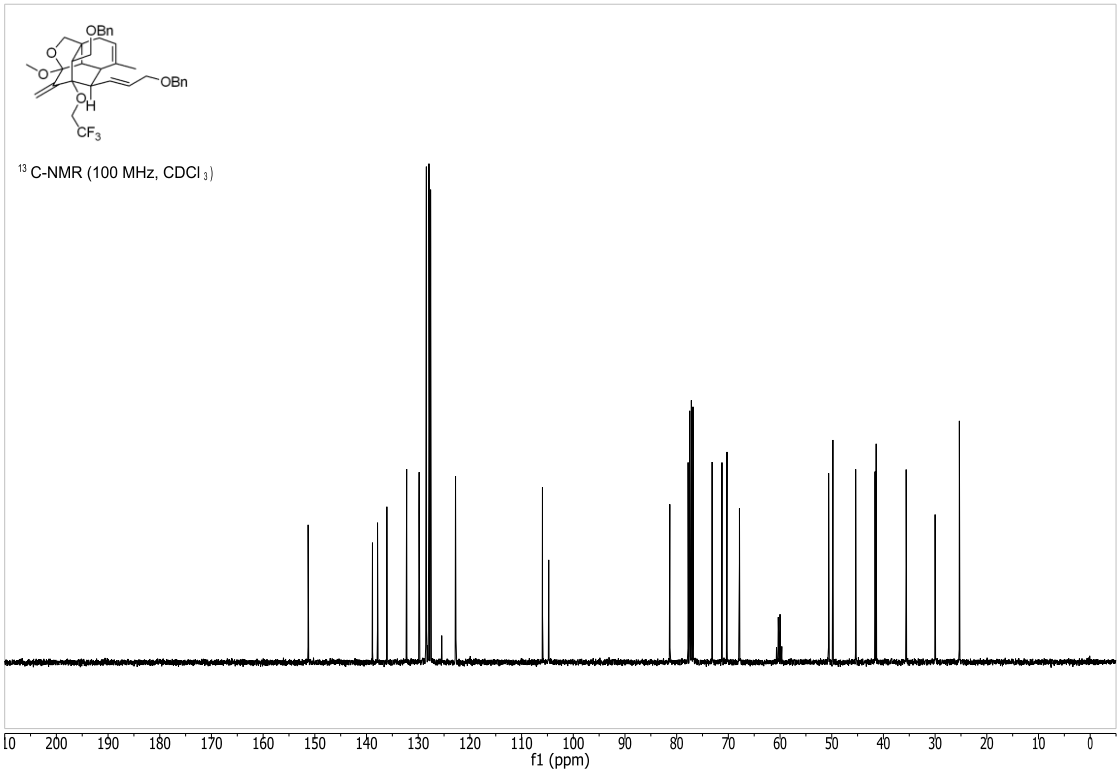
Table A2.3. 2D-NMR Data of Compound **3.28**

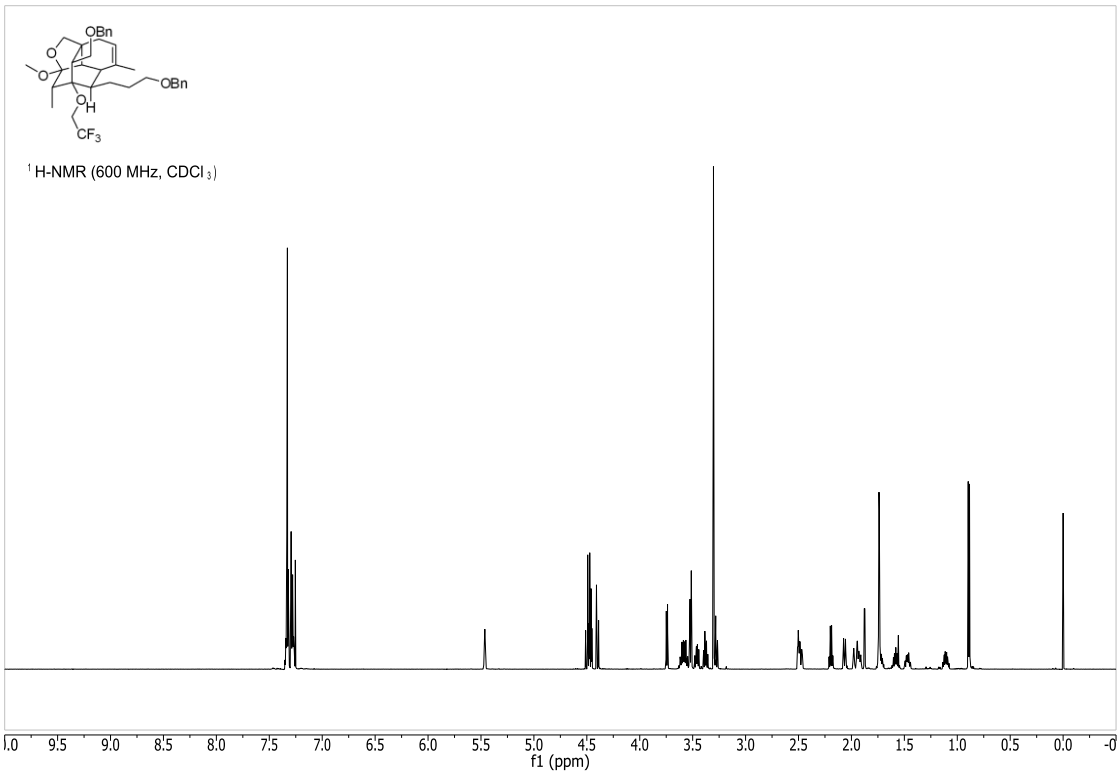


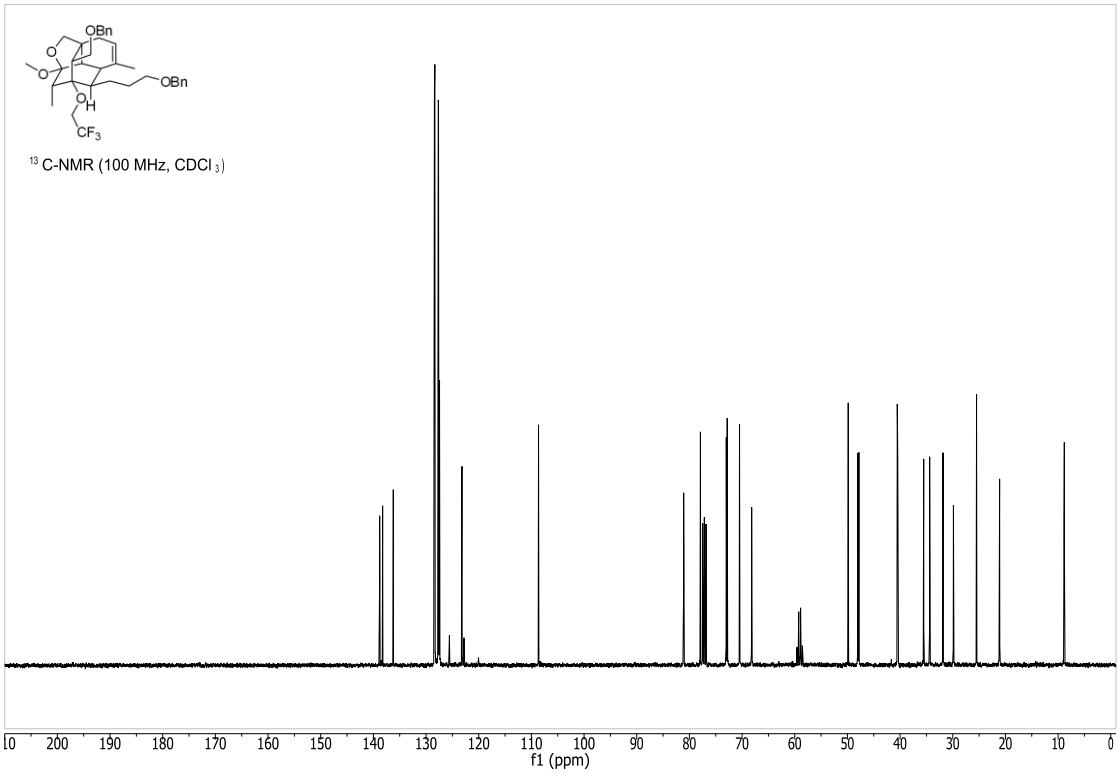
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	NOESY correlations
1	108.77		Cq			
2a	81.06	3.54	CH_2	H-2b	C-9, C-3, C-8	H-15, H-81, H-4
2b		3.77		H-2a	C-1, C-9, C-3	H-8b, H-10, H-9
3	39.00		Cq			
4	40.14	1.88	CH	H-5	C-1, C-2, C-11, C-10, C-4, C-3, C-5, C-8	H-2a, H-15, H-5
5	34.78	2.42	CH	H-7, H-12, H-8a, H-17		H-17, H-4
6	136.05		Cq			
7	122.26	5.44	CH	H-8b, H-8a, H-17		H-28a, H-8b, H-8a, H-17

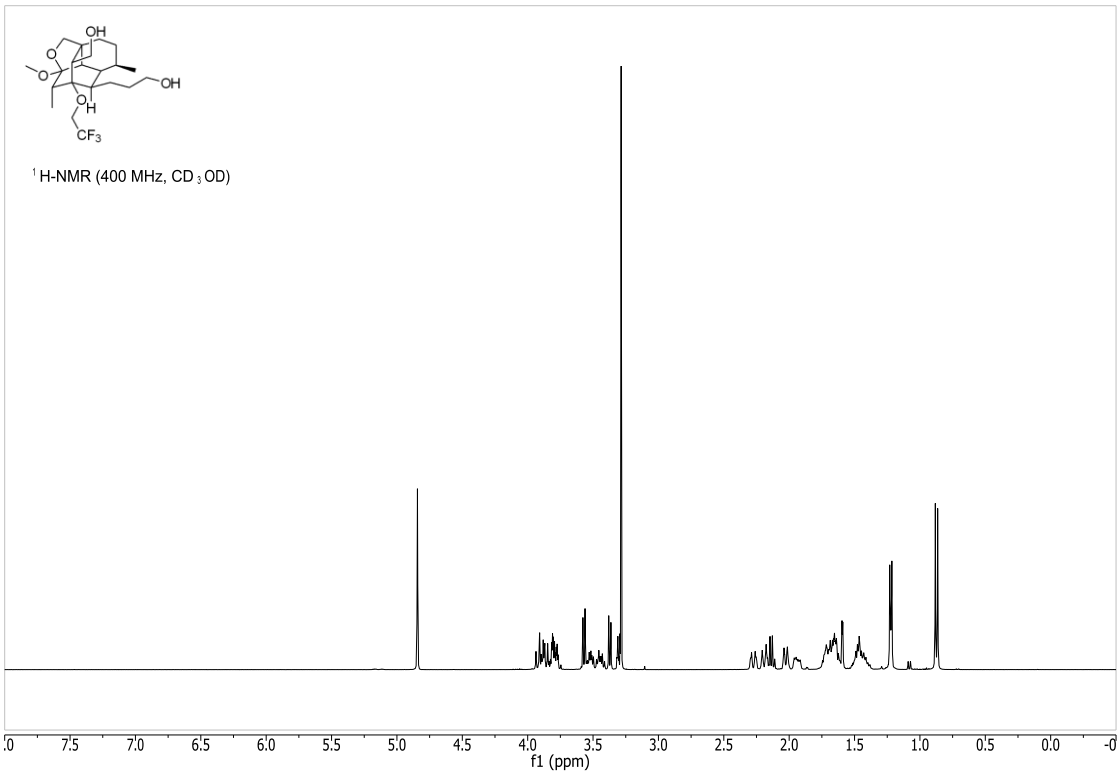
8a	29.77	2.01	CH_2	H-7, H-5, H-17		H-7, H-2a
8b		2.43			C-6, C-7, C-11, C-4, C-3, C-17	H-7, H-28a
9	47.97	2.12	CH	H-28a, H-28b, H-12	C-2, C-11, C-10, C-4, C-3	H-2b
10	47.66	2.24	CH	H-16	C-1, C-11, C-9, C-4, C-3, C-16	H-13b, H-9, H-16
11	77.01		Cq			
12	38.97	2.72	CH	H-18, H-5, H-9	C-6, C-19, C-18, C-11, C-10, C-5	H-19, H-18, H-5, H-16
13a	59.23	3.55	CH_2		C-14	H-10
13b		3.61			C-14	H-10, H-16
14	124.03		Cq			
15	49.87	3.32	CH_3		C-1	H-4, H-16
16	9.07	0.96	CH_3	H-10	C-1, C-11, C-10	H-13b, H-15, H-12,H- 5, H-10
17	25.26	1.66	CH_3	H-7, H-5, H-8a	C-6, C-7, C-5	H-7, H-18, H-5
18	130.47	5.27	CH	H-19, H-20a, H-20b, H-12	C-20, C-12, C-5	H-20a, H-20b, H-28b, H-28a, H-12, H-17
19	131.73	5.62	CH	H-18, H-20a, H-20b, H-12	C-20, C-12	H-12
20a	70.42	3.96	CH_2	H-19, H-18	C-19, C-18, C-21	H-18, H-19
20b		4.02		H-19. H-18	C-19, C-18, C-21	H-18, H-19
21a	71.08	4.42	CH_2		C-22, C-23, C-27, C-20	H-23, H-27, H-20a, H-20b
21b		4.49			C-22, C-23, C-27, C-20	H-23, H-27, H-20a, H-20b
22	138.94		Cq			
23	127.50	7.34	CH			
24	128.50		CH			
25	127.50		CH			
26	128.50		CH			
27	127.50	7.34	CH			
28a	68.32	3.36	CH_2	H-9, H-28b	C-29, C-9, C-3	H-18, H-29a, H-29b, H-9
28b		3.5		H-9, H-28a	C-11, C-29, C-9, C-3	H-18, H-29a, H-29b, H-9, H-8b
29a	73.11	4.37	CH_2		C-30, C-31, C-35, C-28	H-31, H-35, H-28a, H-28b
29b		4.44			C-30, C-31, C-35, C-28	H-31, H-35, H-28a, H-28b
30	138.07		Cq			
31	127.77	7.26	CH			
32	127.86		CH			
33	127.77		CH			
34	127.86		CH			
35	127.77	7.26	CH			

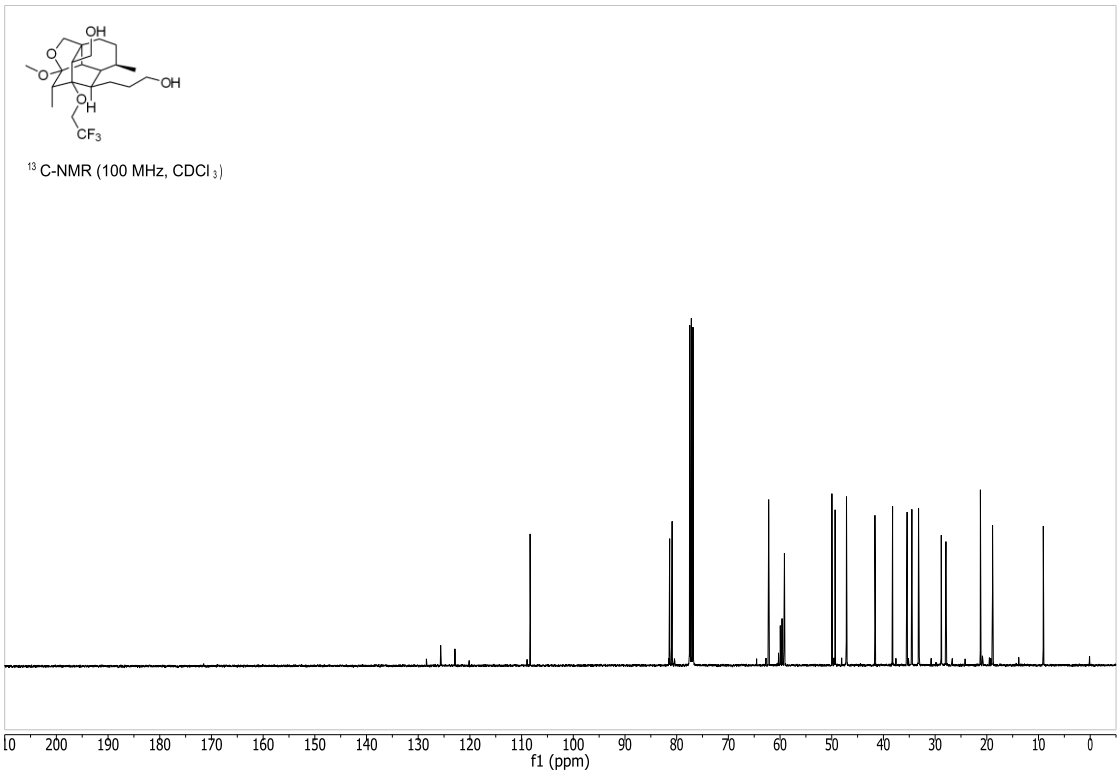

OBn
OBn
O
O
H
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

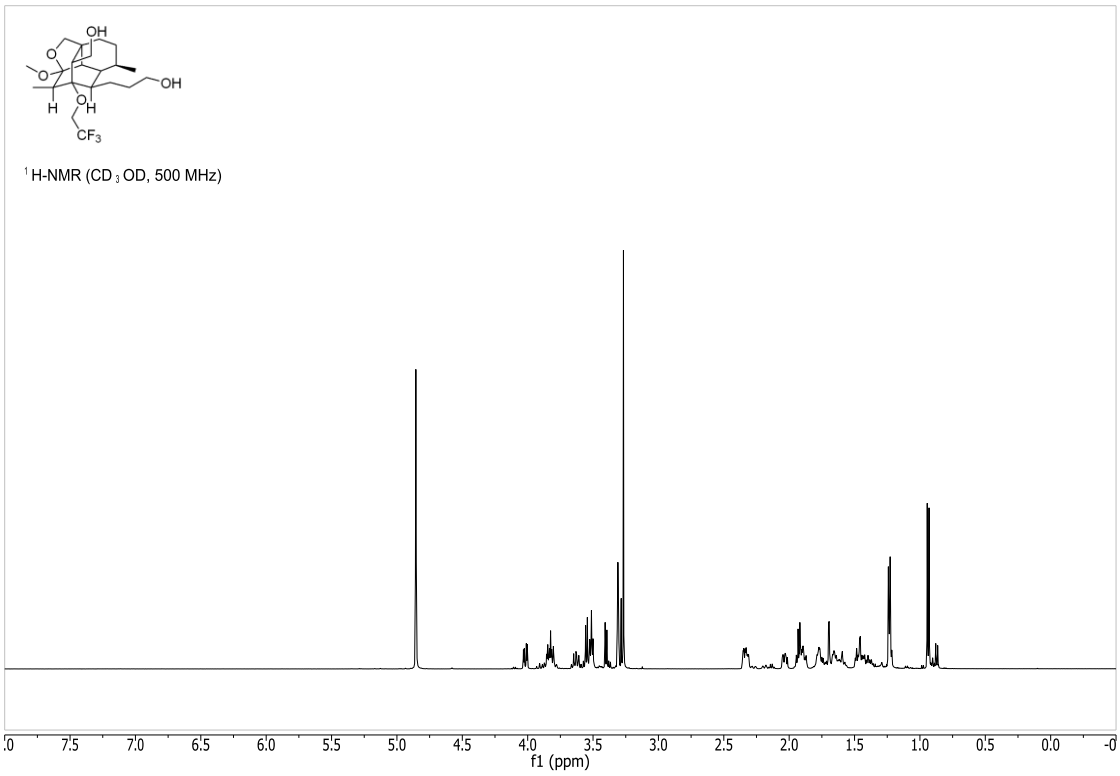

OBn
OBn
O
O
H
CF3
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

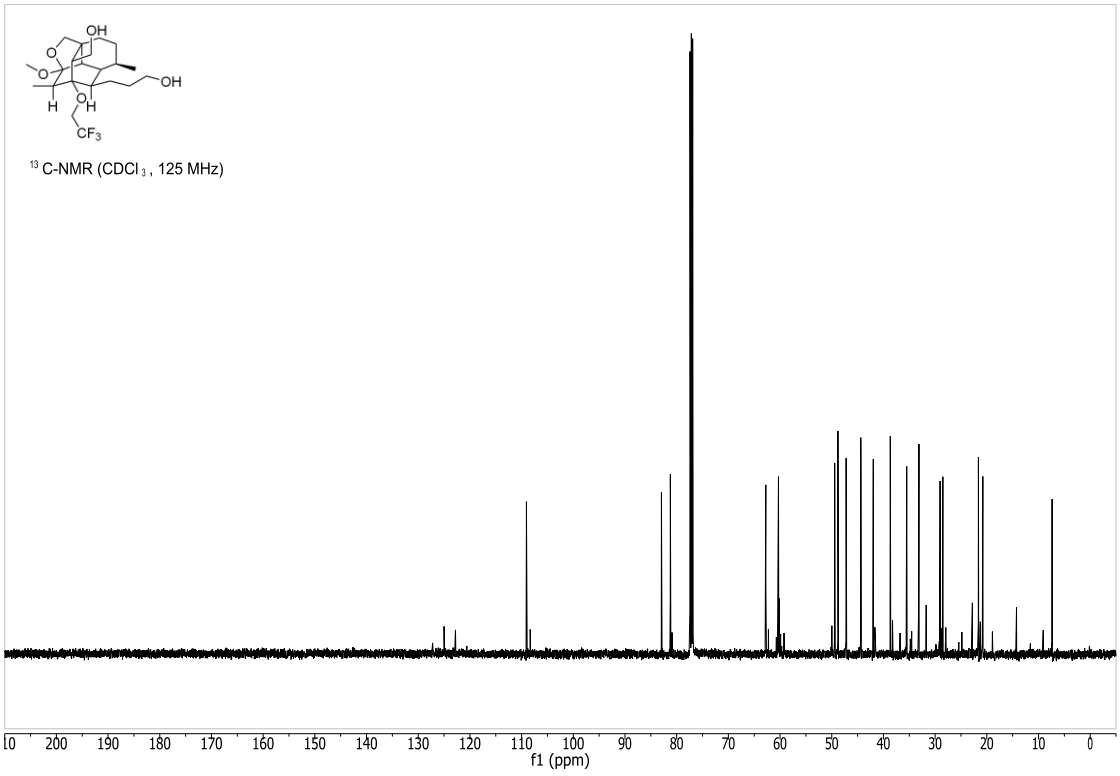

OBn
O
O
OBn
O
H
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

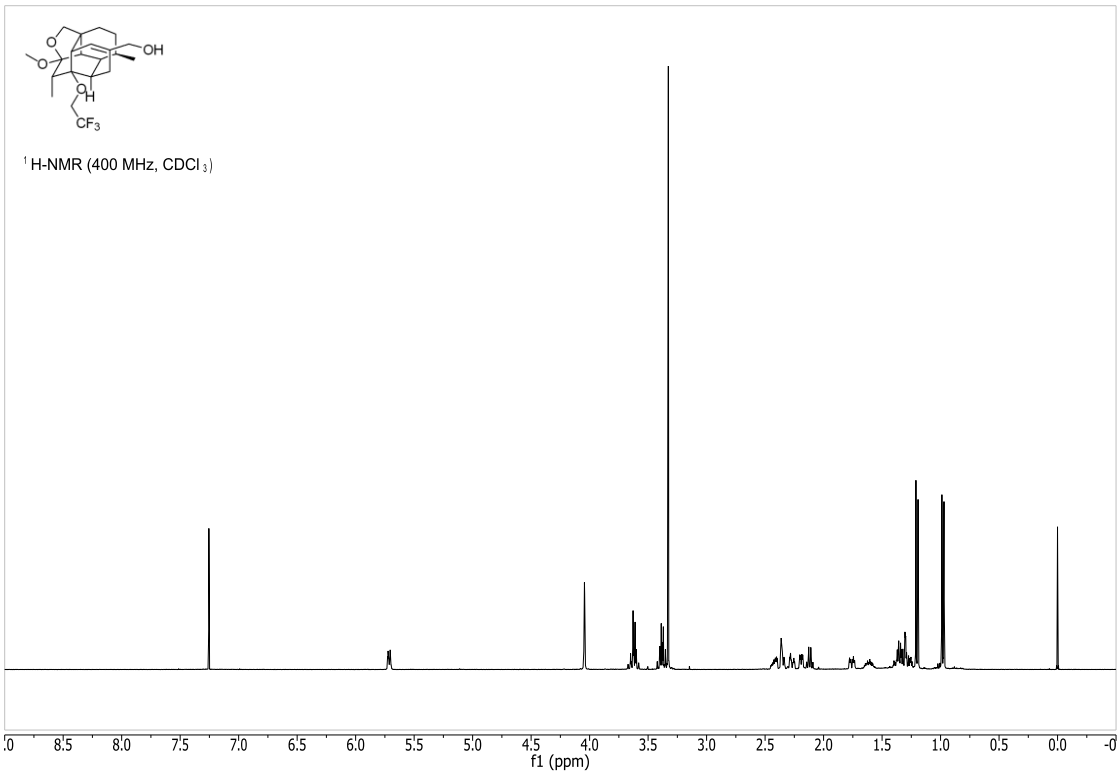

OBn
O
O
OBn
O
H
CF3
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

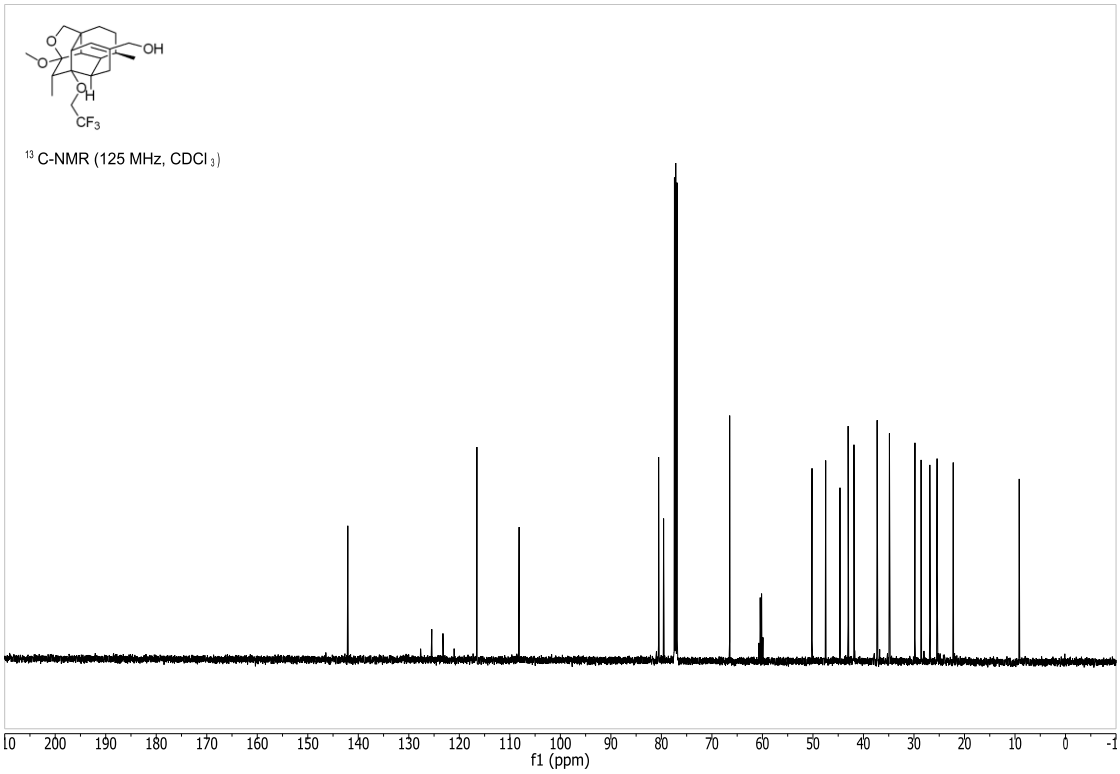

OH
O
O
OH
O
H
CF3
1 H-NMR (400 MHz, CD 3 OD)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

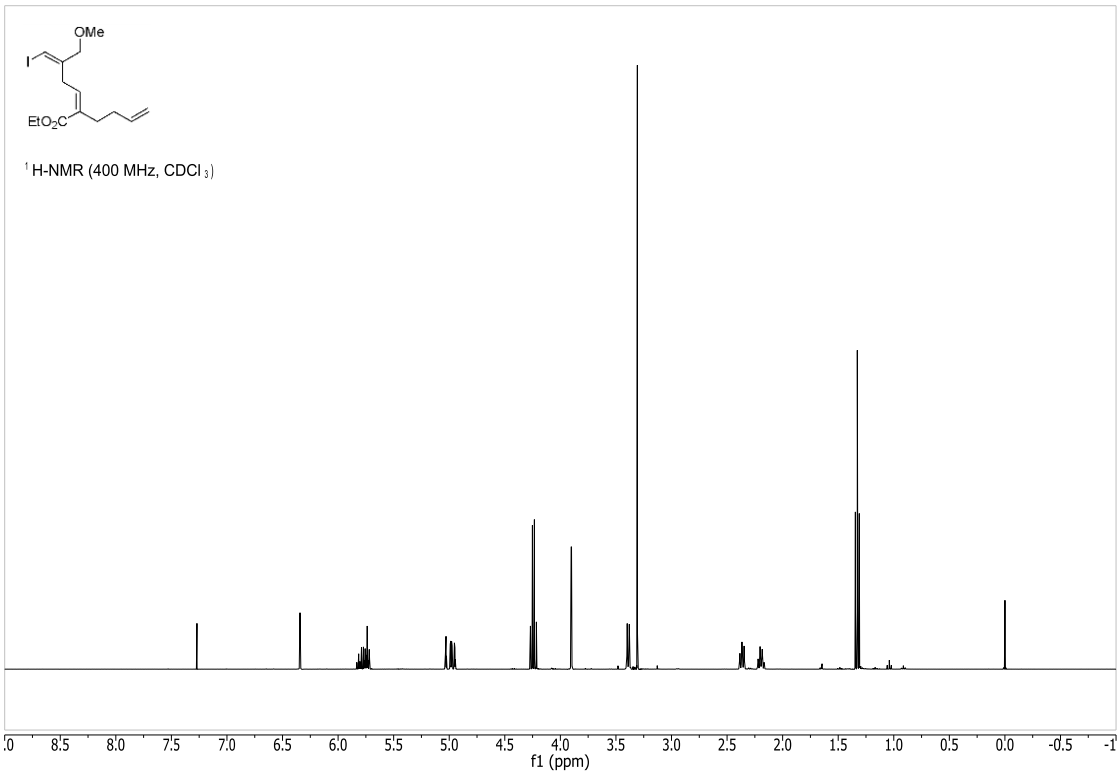

OH
O
O
OH
O
H
CF3
13 C-NMR (100 MHz, CDCl 3)
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

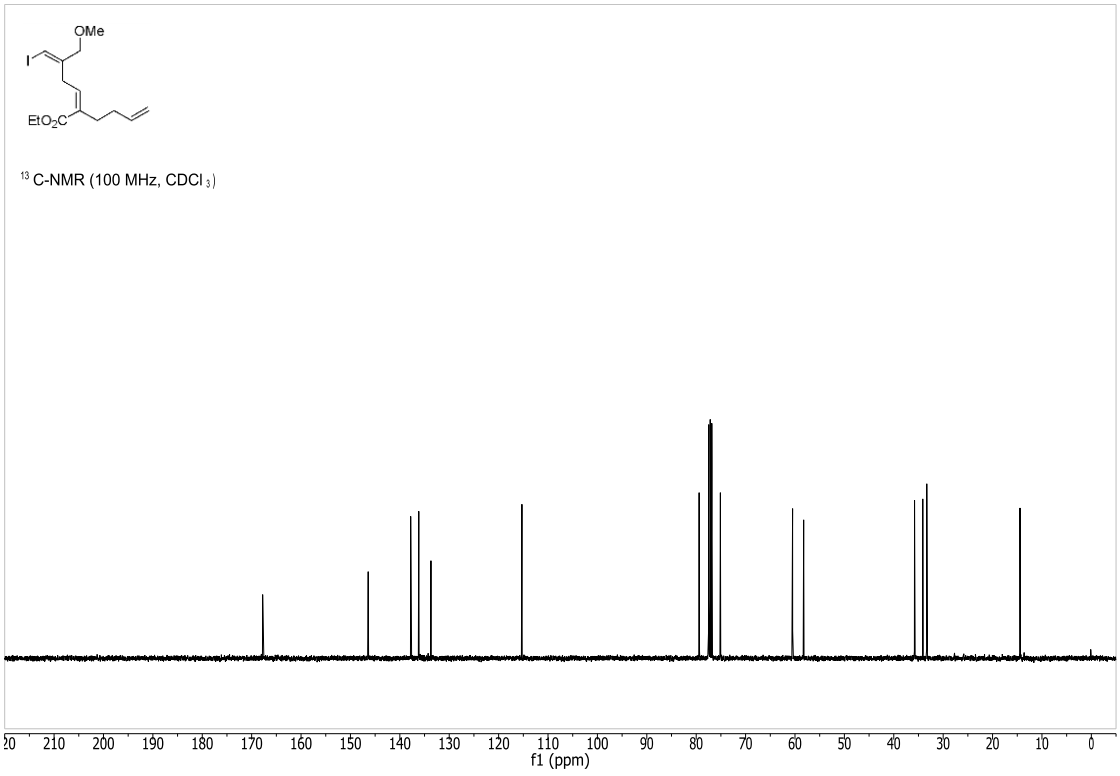

OH
O
O
OH
H
O
H
CF3
1 H-NMR (CD 3 OD, 500 MHz)
f1 (ppm)

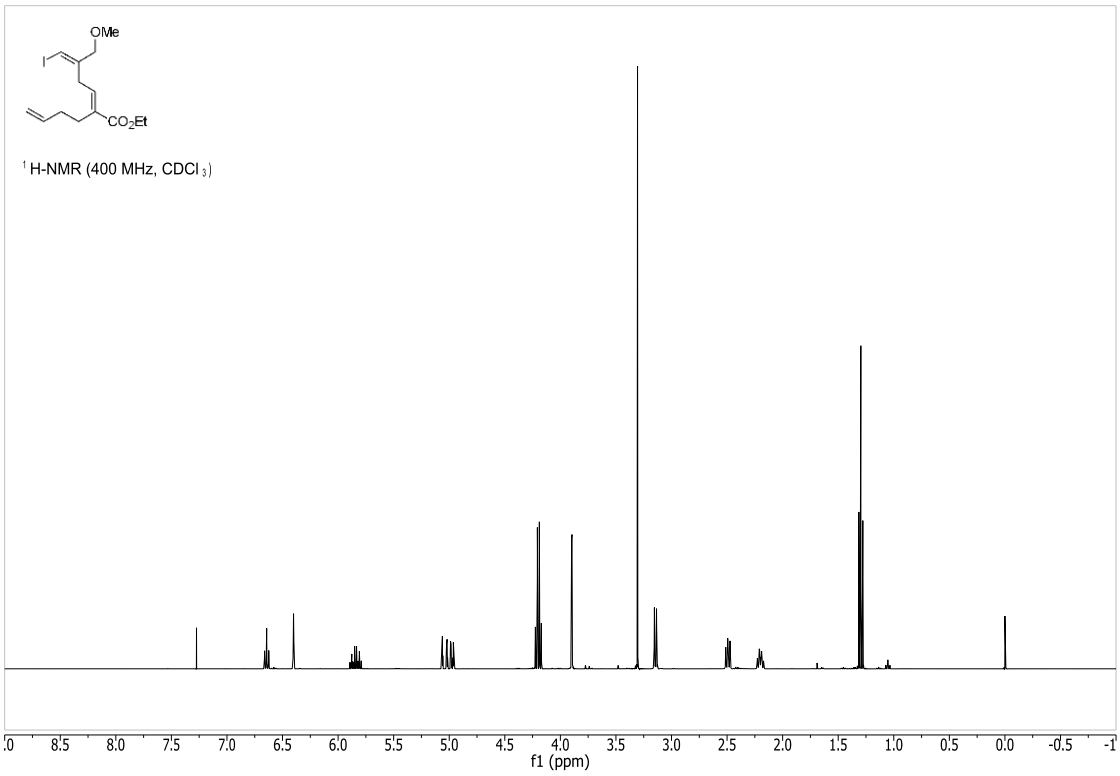

OH
O
O
OH
H
O
H
CF3
13 C-NMR (CDCl 3 , 125 MHz)
f1 (ppm)

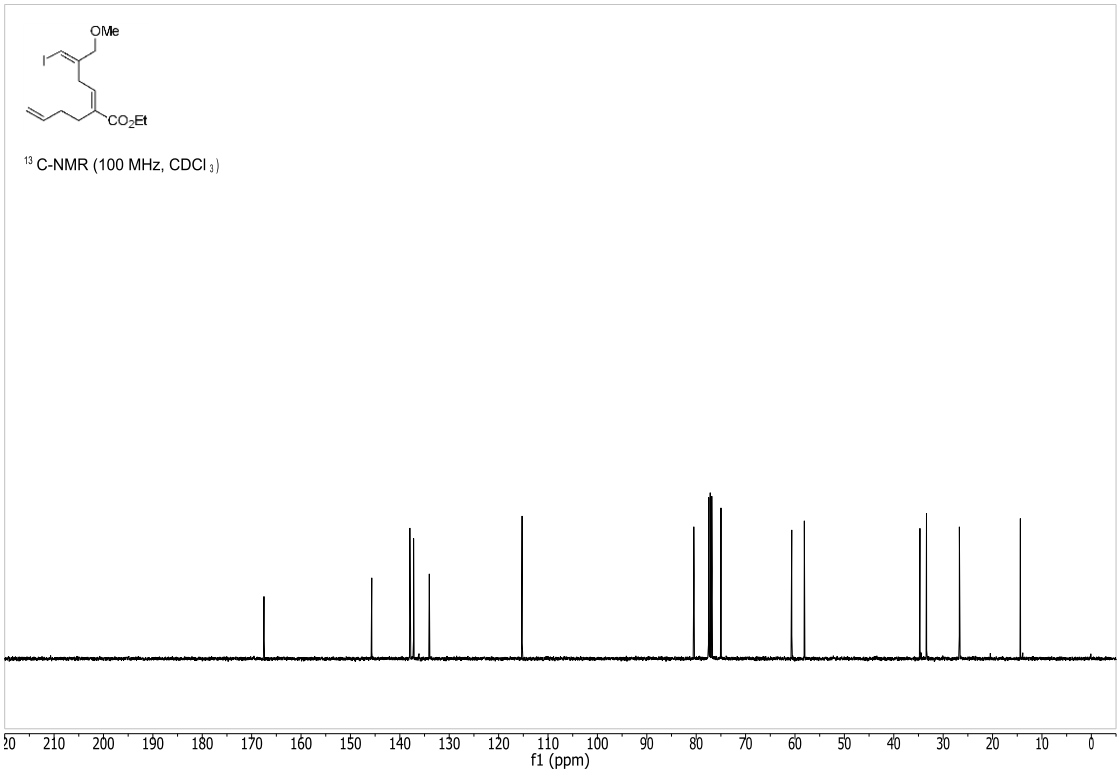

OH
O
O
H
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

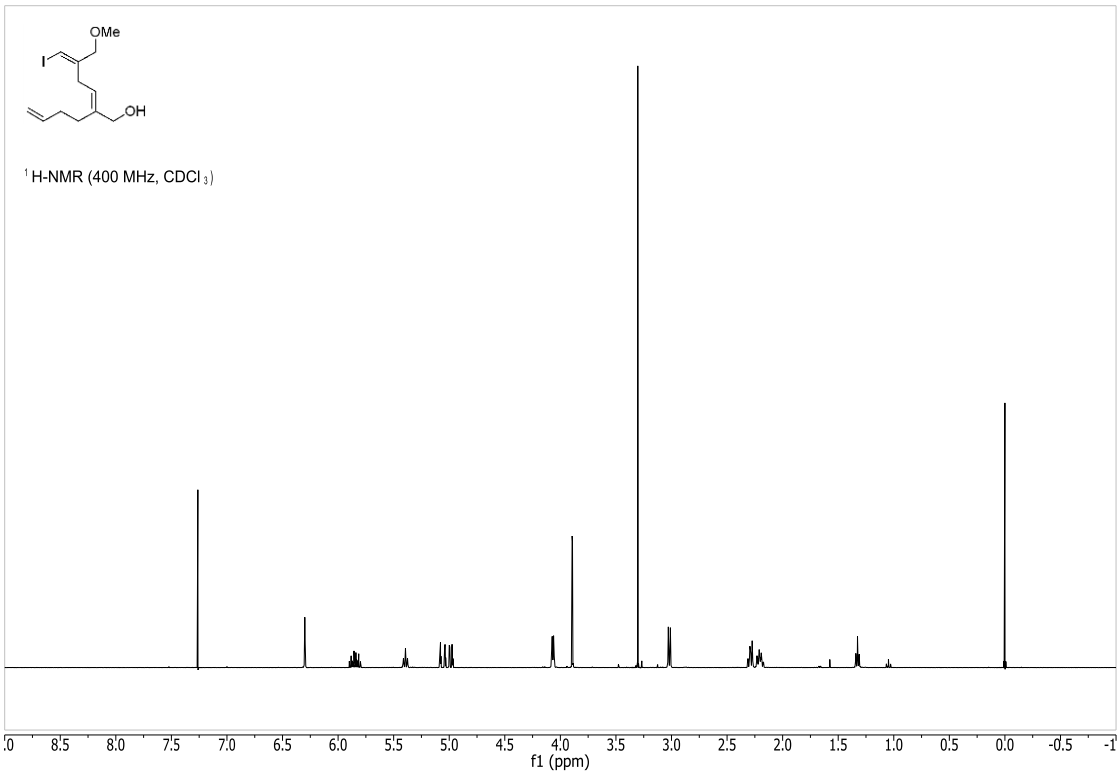

OH
O
O
H
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

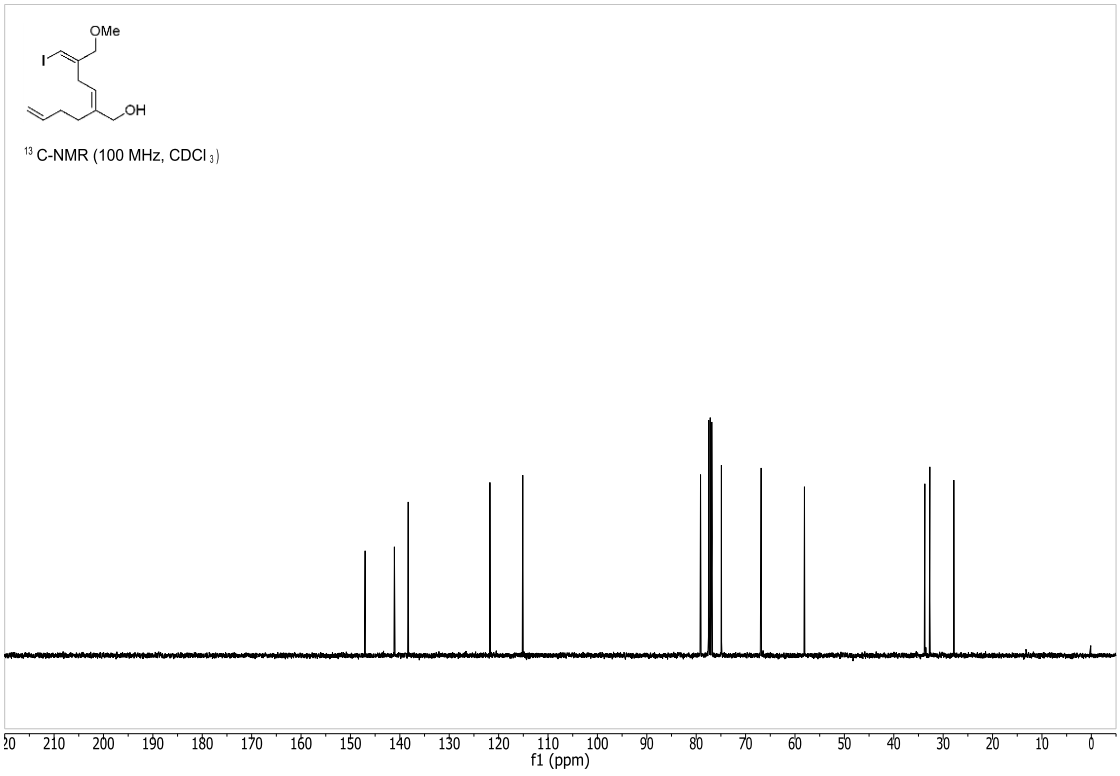

OMe
I
EtO2C
1 H-NMR (400 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

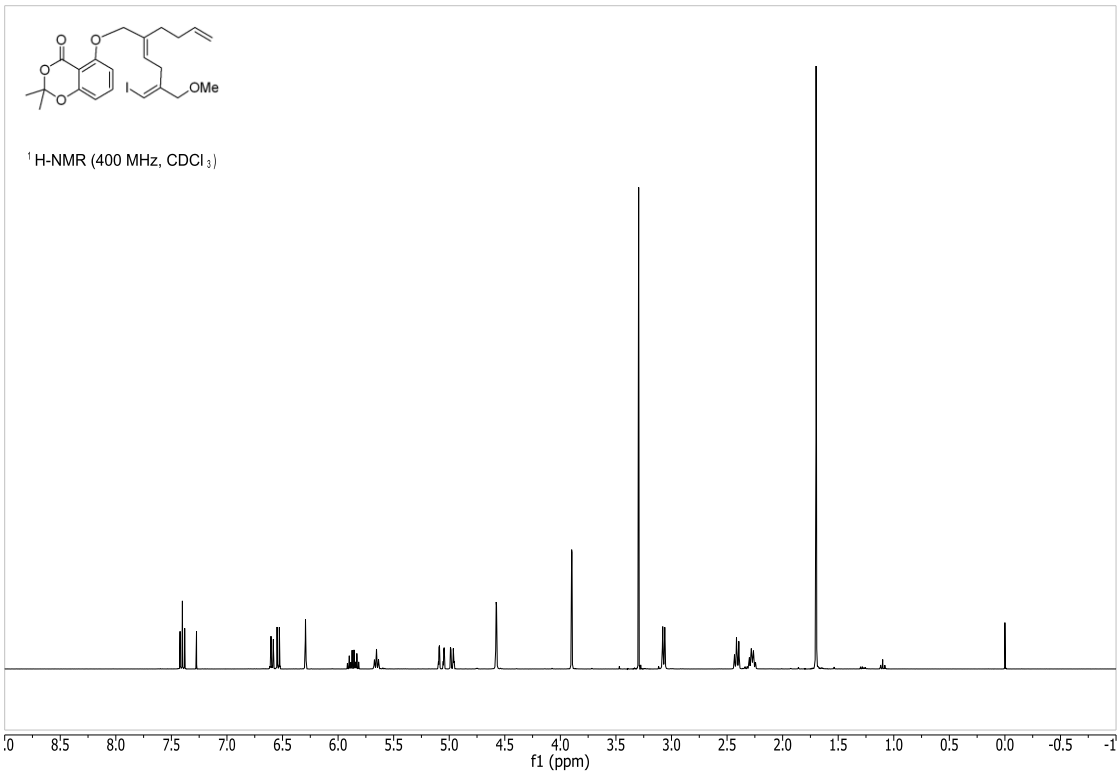

OMe
I
EtO2C
13 C-NMR (100 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

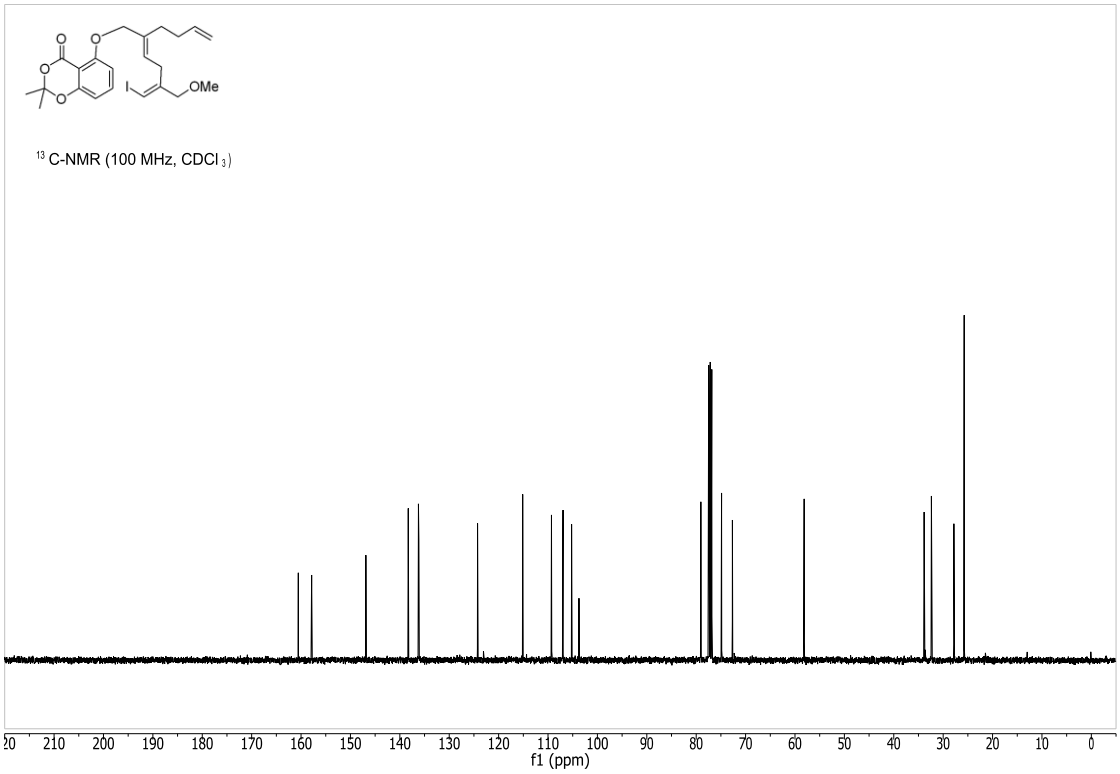

OMe
I
CO2Et
1 H-NMR (400 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

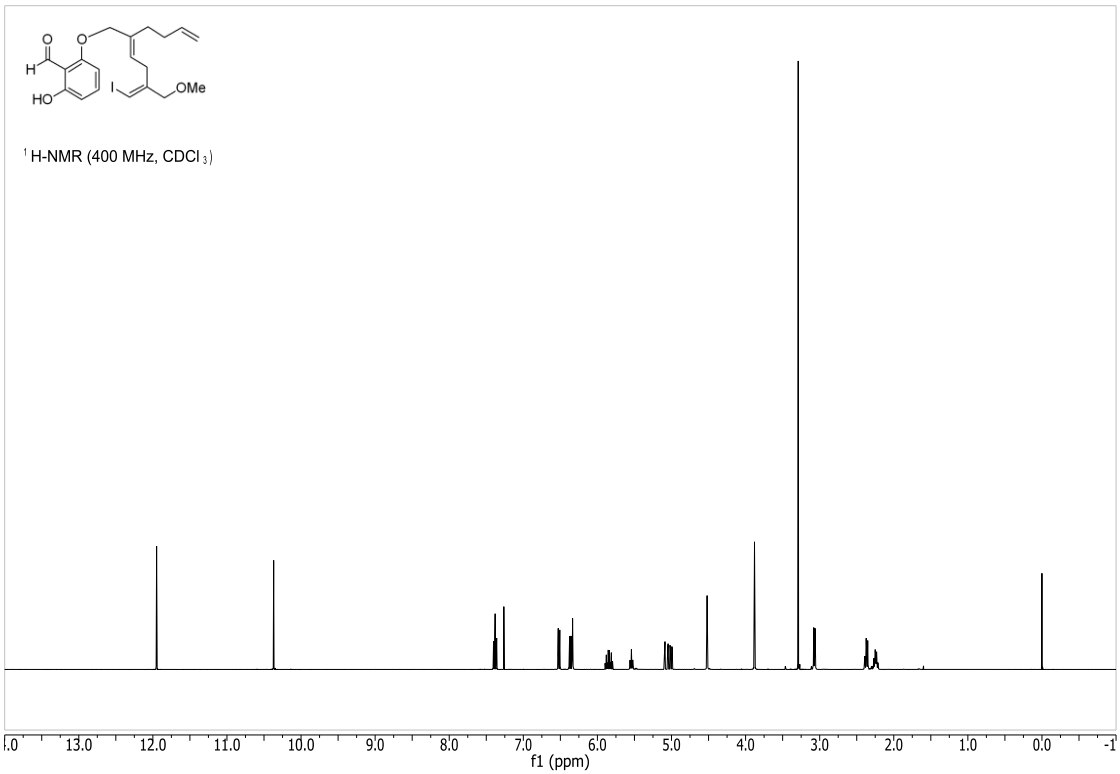

OMe
I
CO2Et
13 C-NMR (100 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

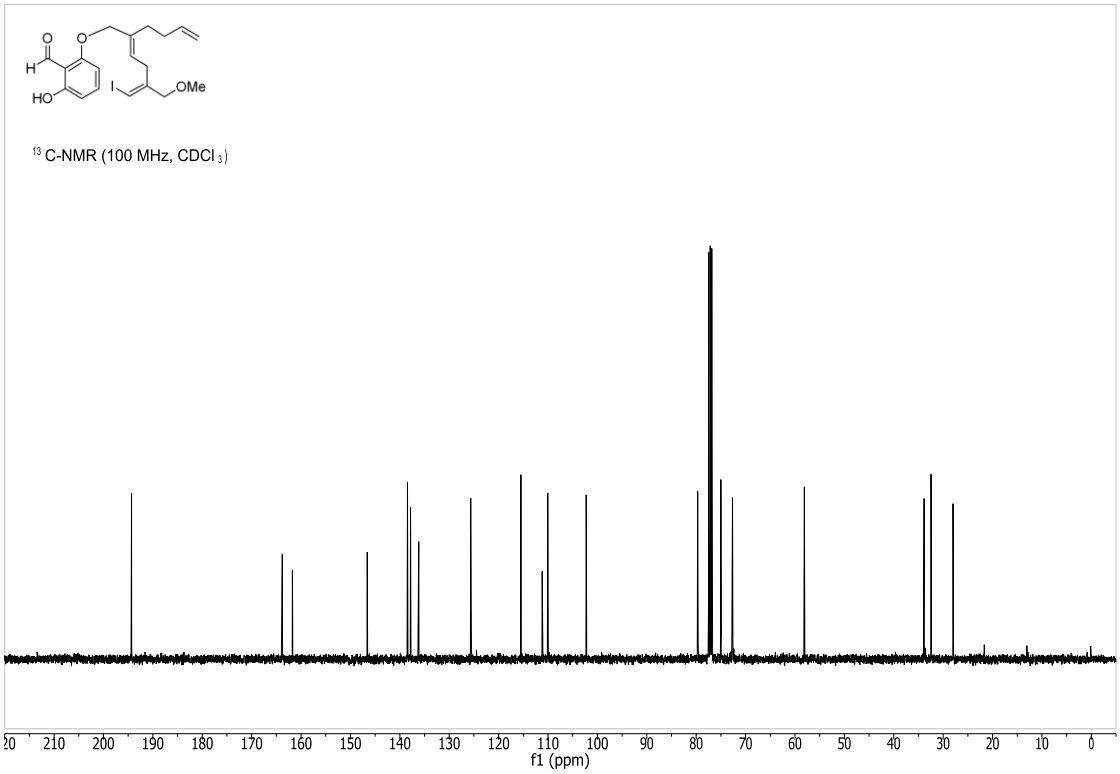

OMe
I
OH
1 H-NMR (400 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

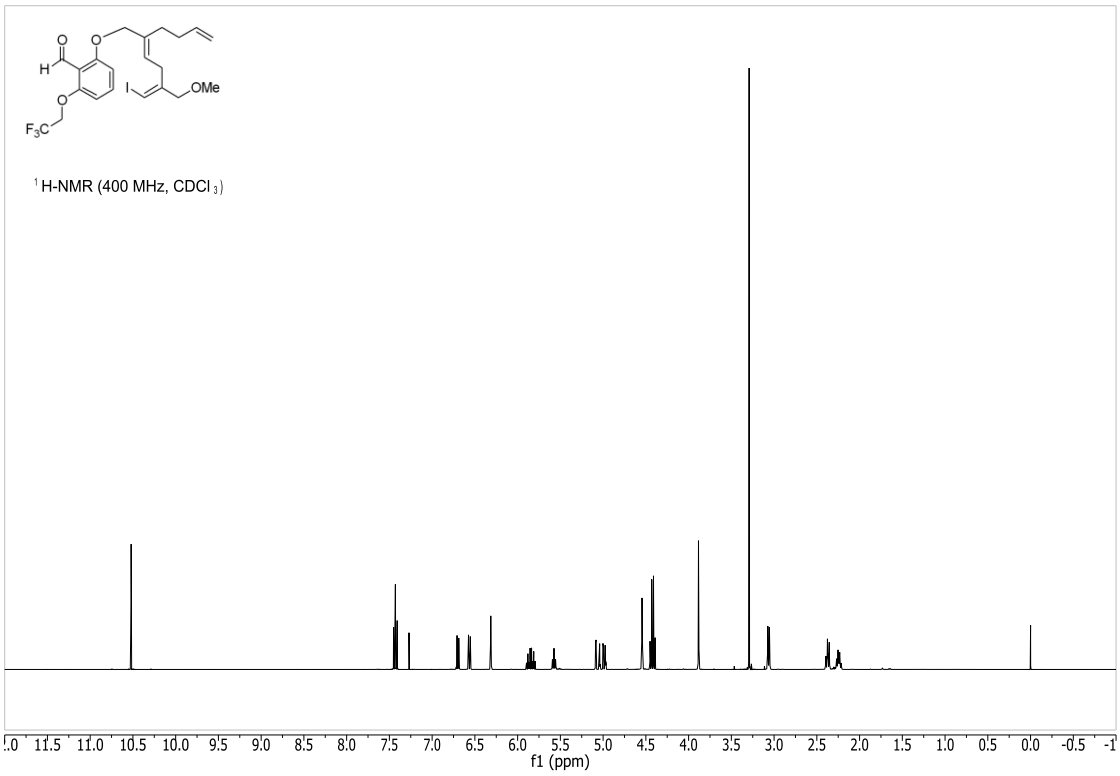

OMe
I
OH
13 C-NMR (100 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

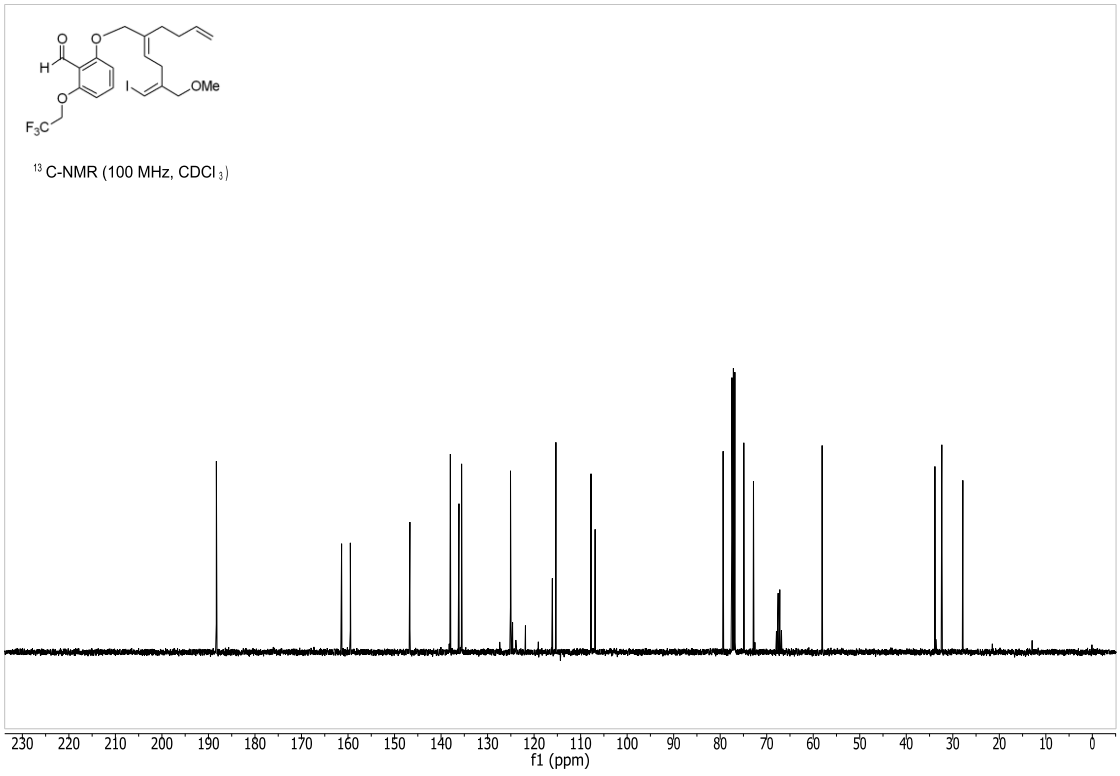

OMe
1 H-NMR (400 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

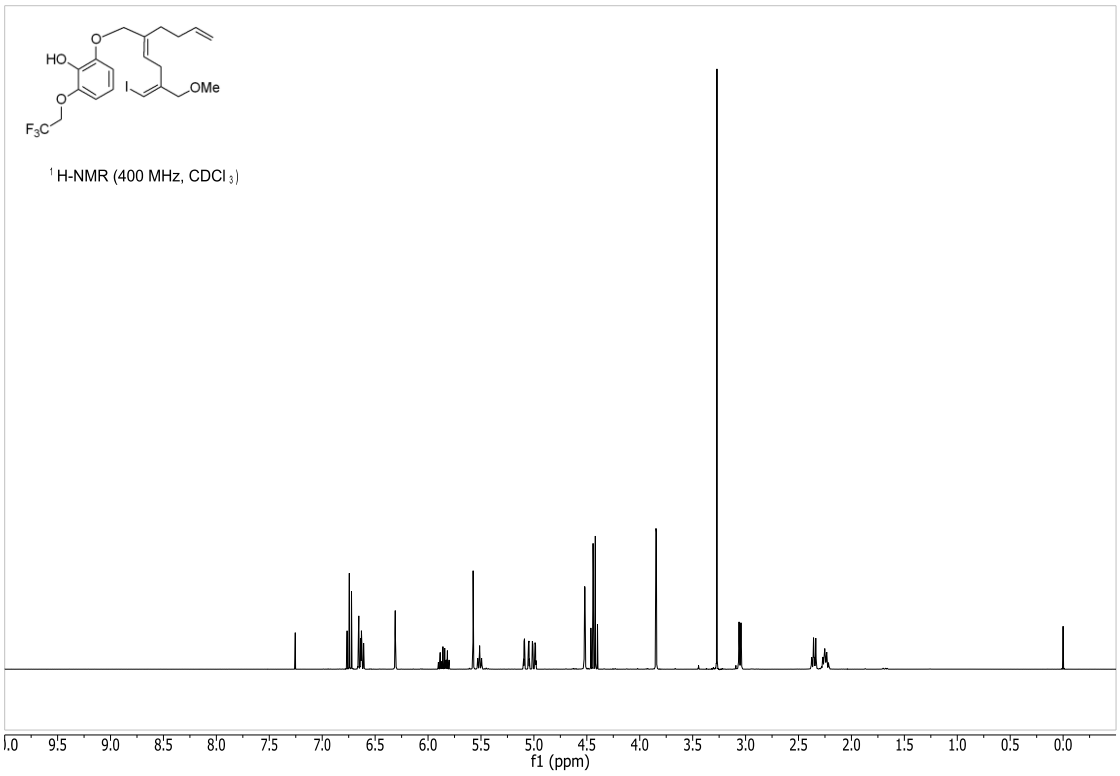

OMe
13 C-NMR (100 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

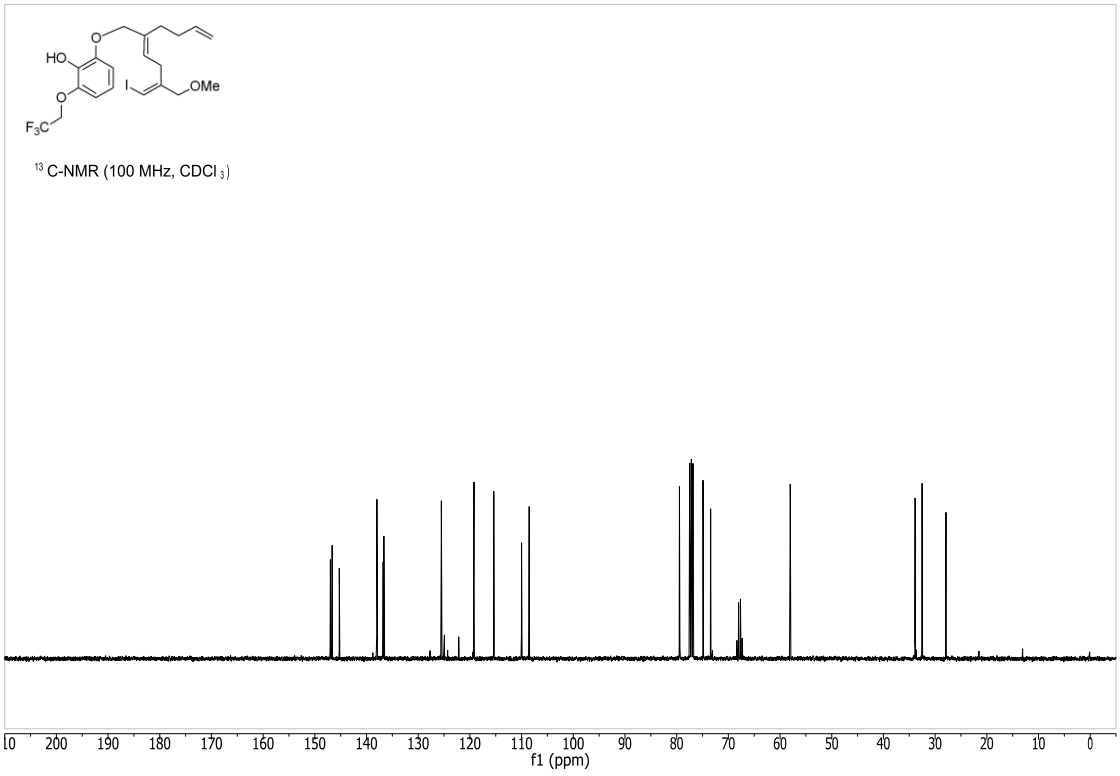

O
H
O
HO
I
OMe
1 H-NMR (400 MHz, CDCl 3)
13.0
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
f1 (ppm)

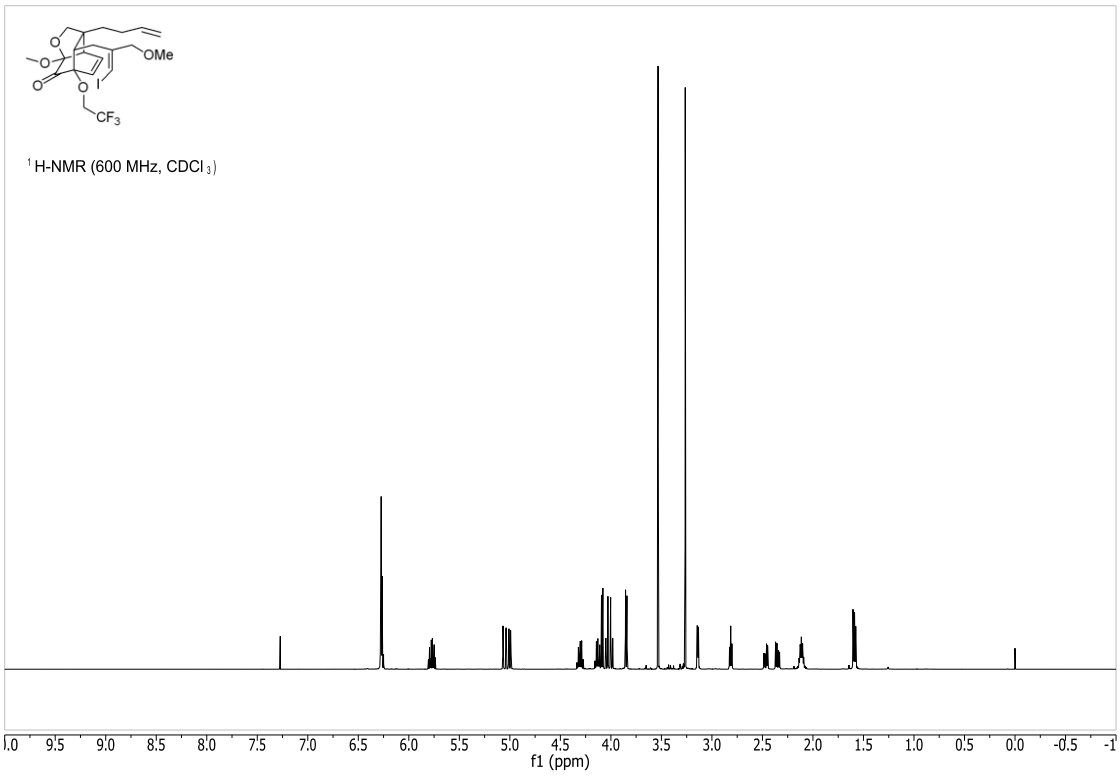

O
H
O
HO
I
OMe
13 C-NMR (100 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

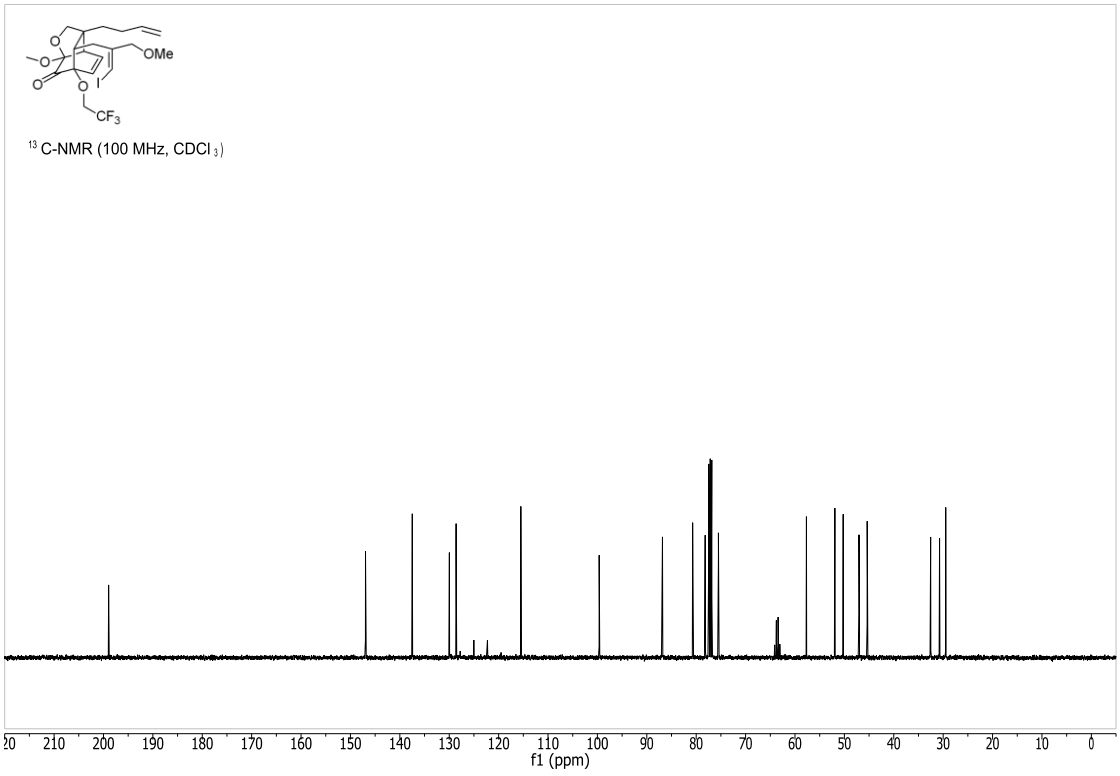

O
H
O
I
OMe
O
F3C
1 H-NMR (400 MHz, CDCl 3)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

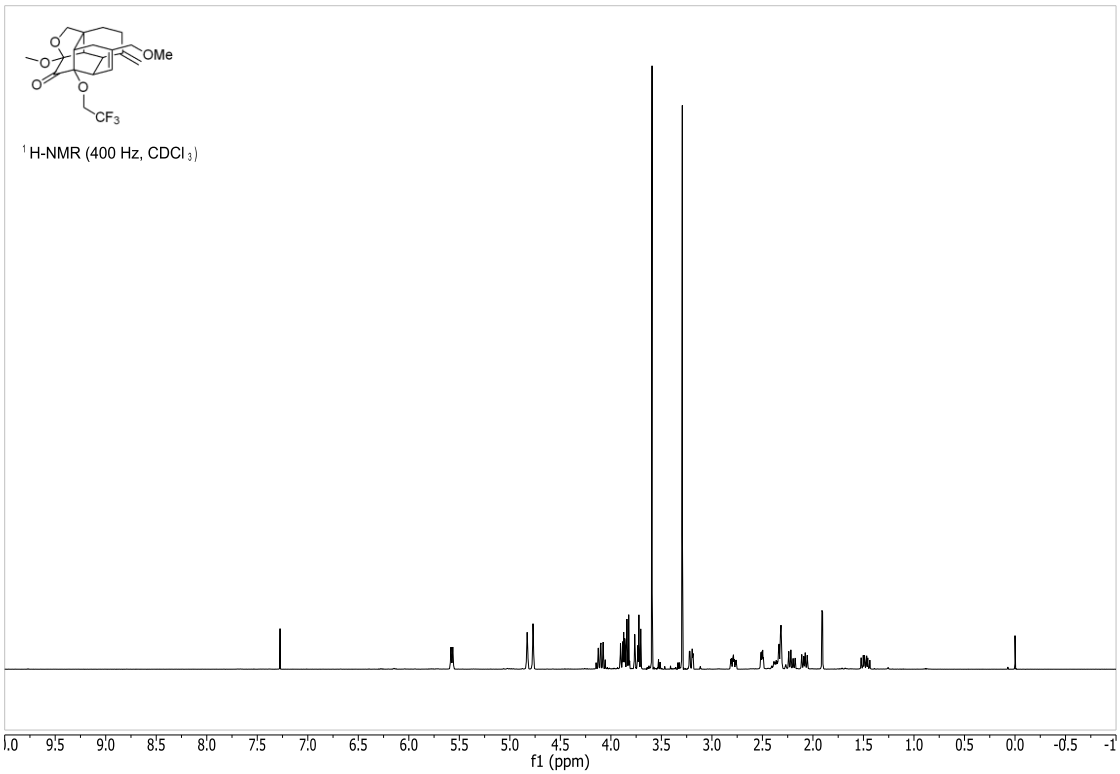

O
H
O
I
OMe
O
F3C
13 C-NMR (100 MHz, CDCl 3)
230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

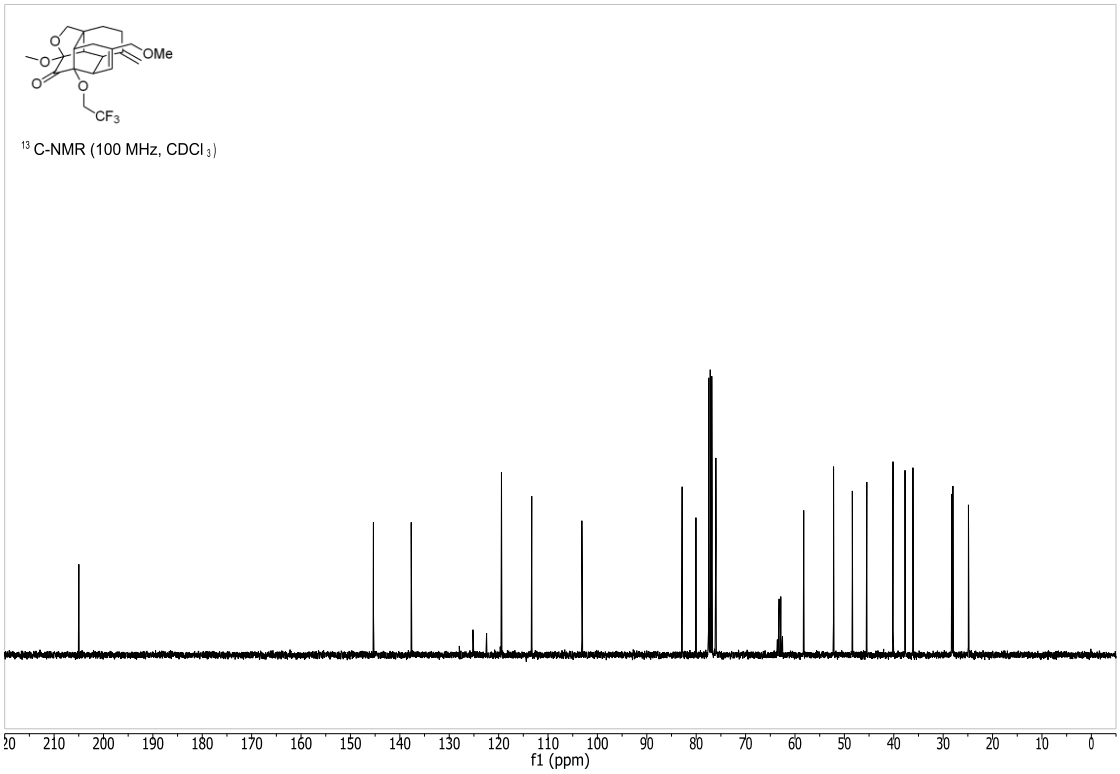

HO
O
O
F3C
I
OMe
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)


HO
O
O
F3C
I
OMe
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)


OMe
I
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)


OMe
I
CF3
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)


OMe
CF3
1H-NMR (400 Hz, CDCl3)
f1 (ppm)


OMe
CF3
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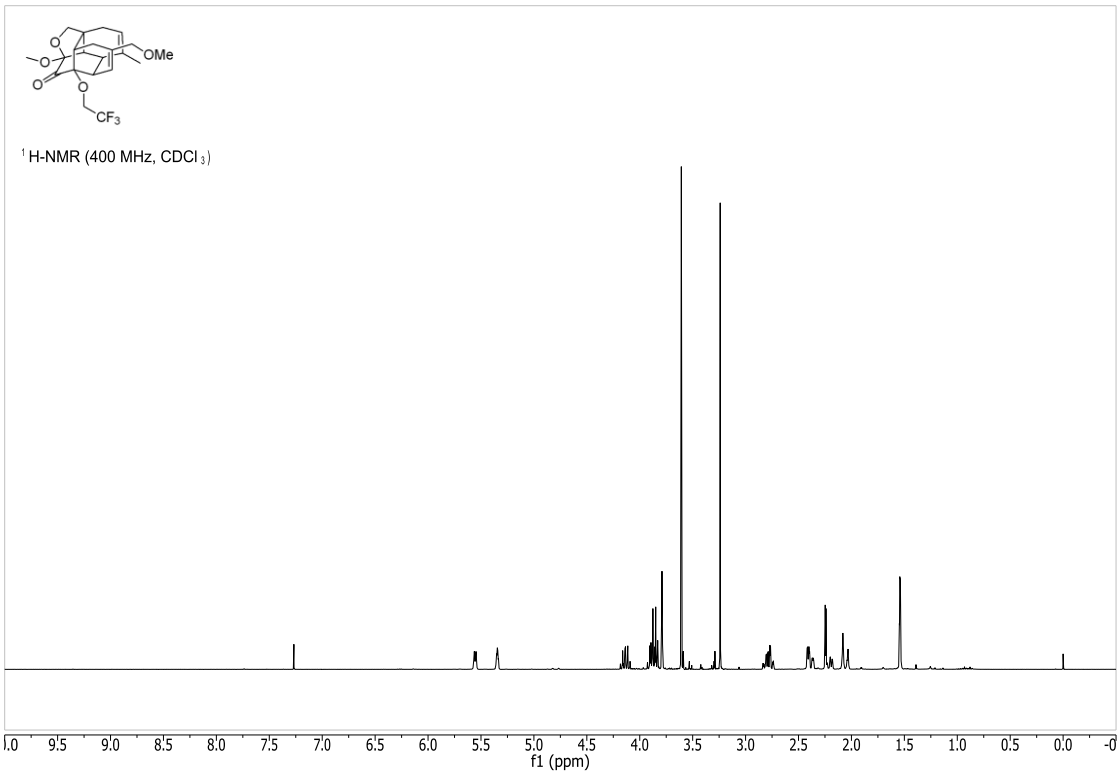
f1 (ppm)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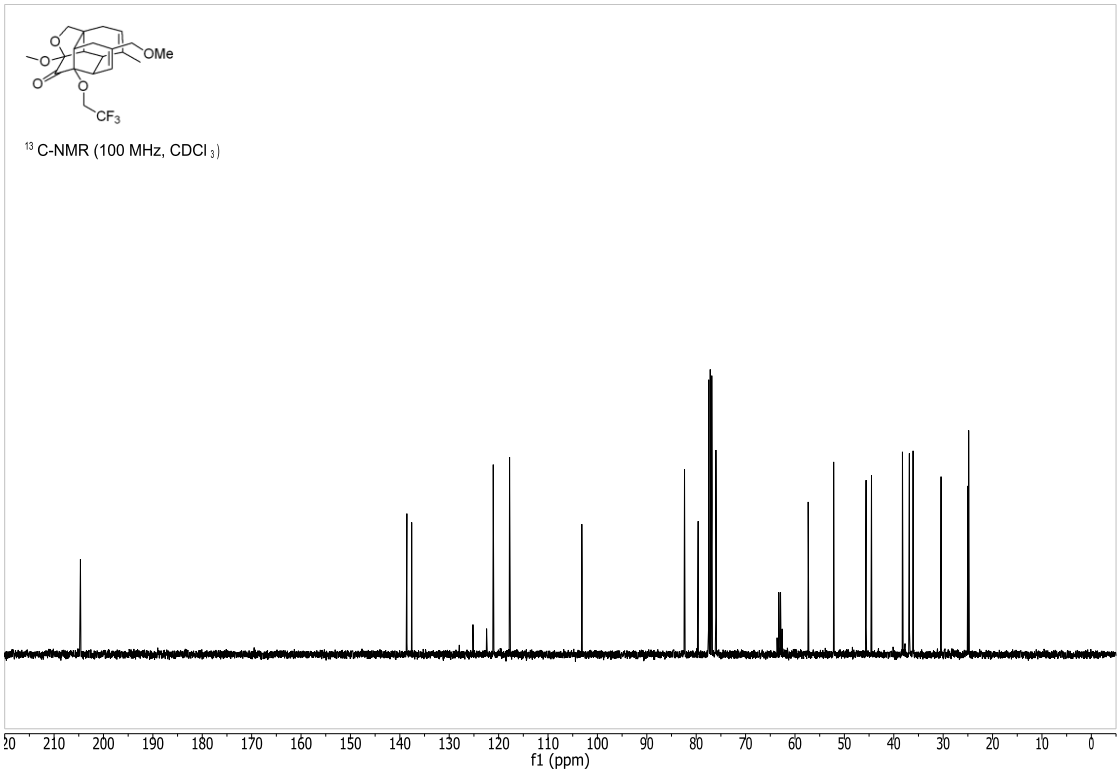
O
O
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)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CF3
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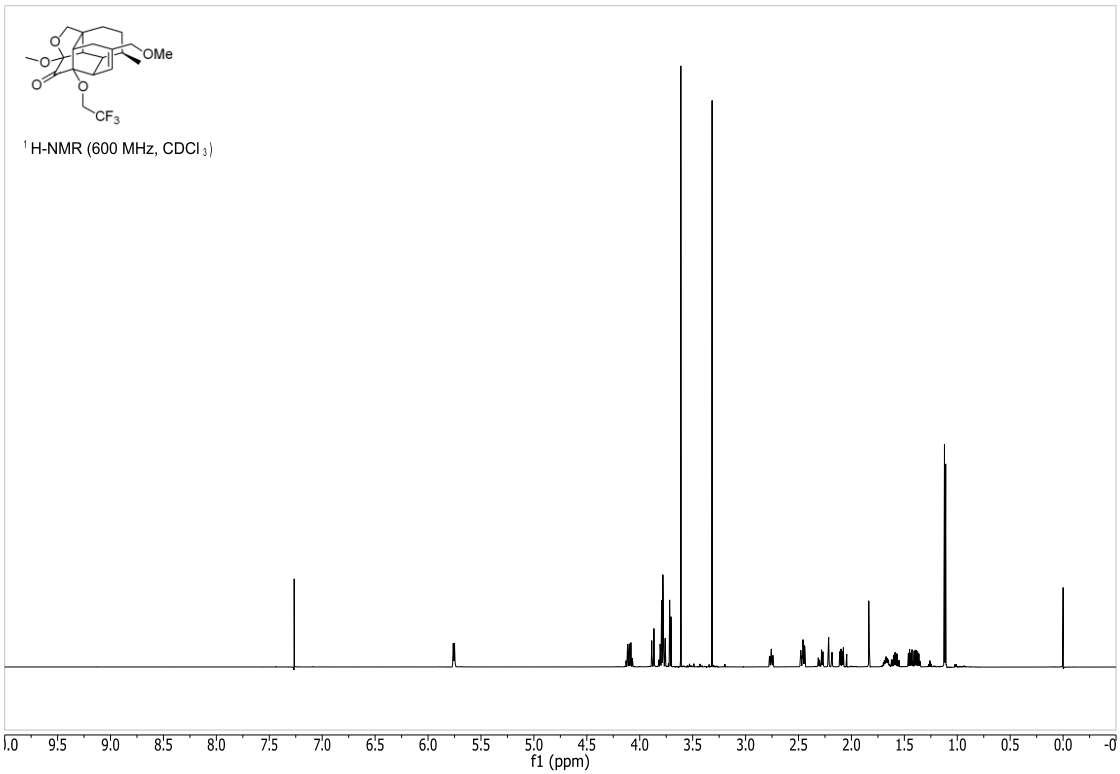
f1 (ppm)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CF3
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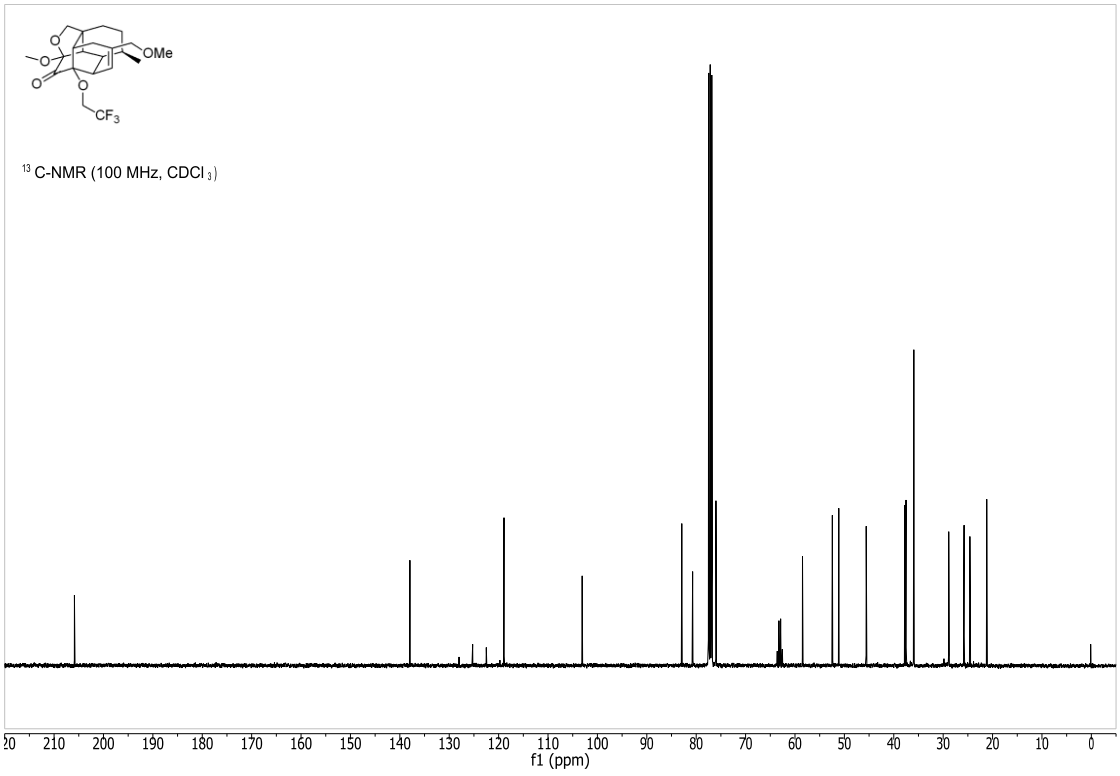
f1 (ppm)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CF3
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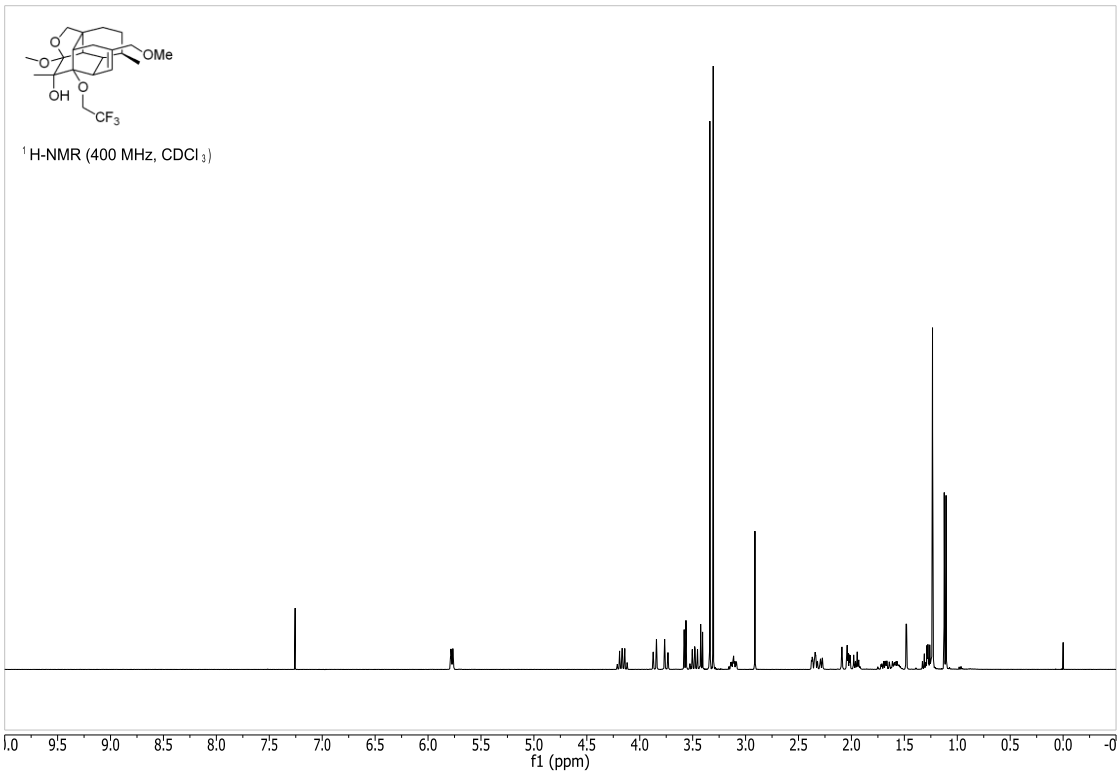
f1 (ppm)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O
CF3
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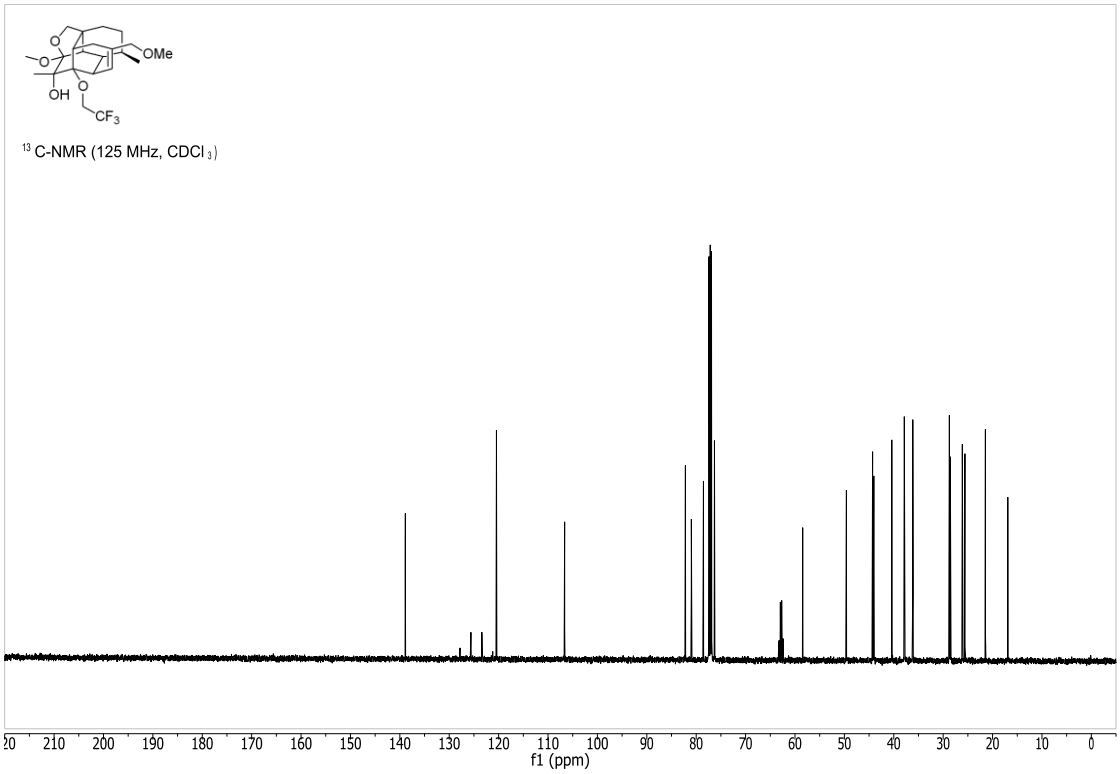
f1 (ppm)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O
CF3
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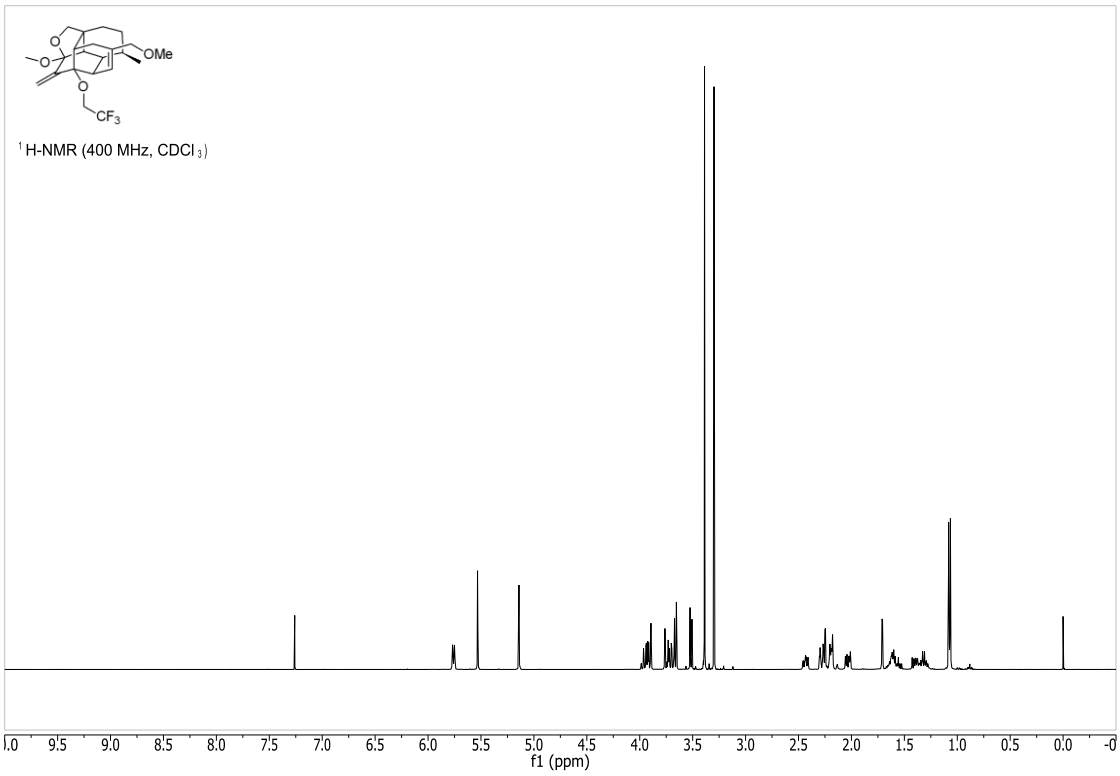
f1 (ppm)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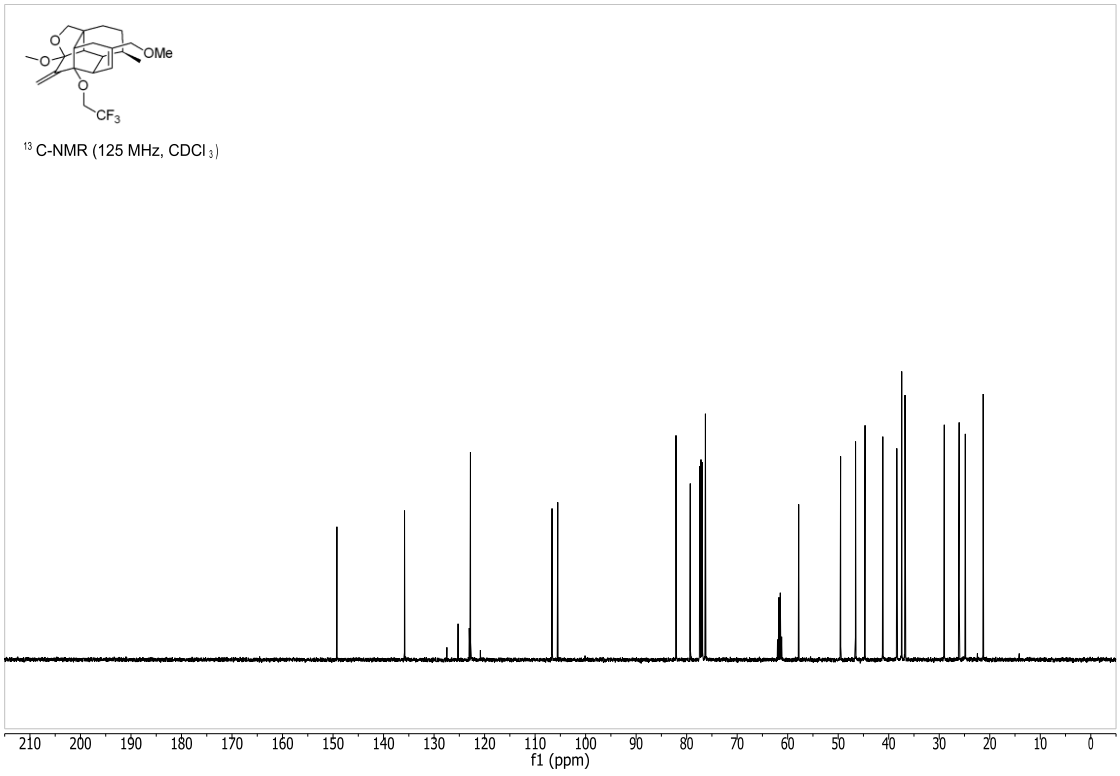
O
O
CF3
1H-NMR (400 MHz, CDCl3)
f1 (ppm)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CF3
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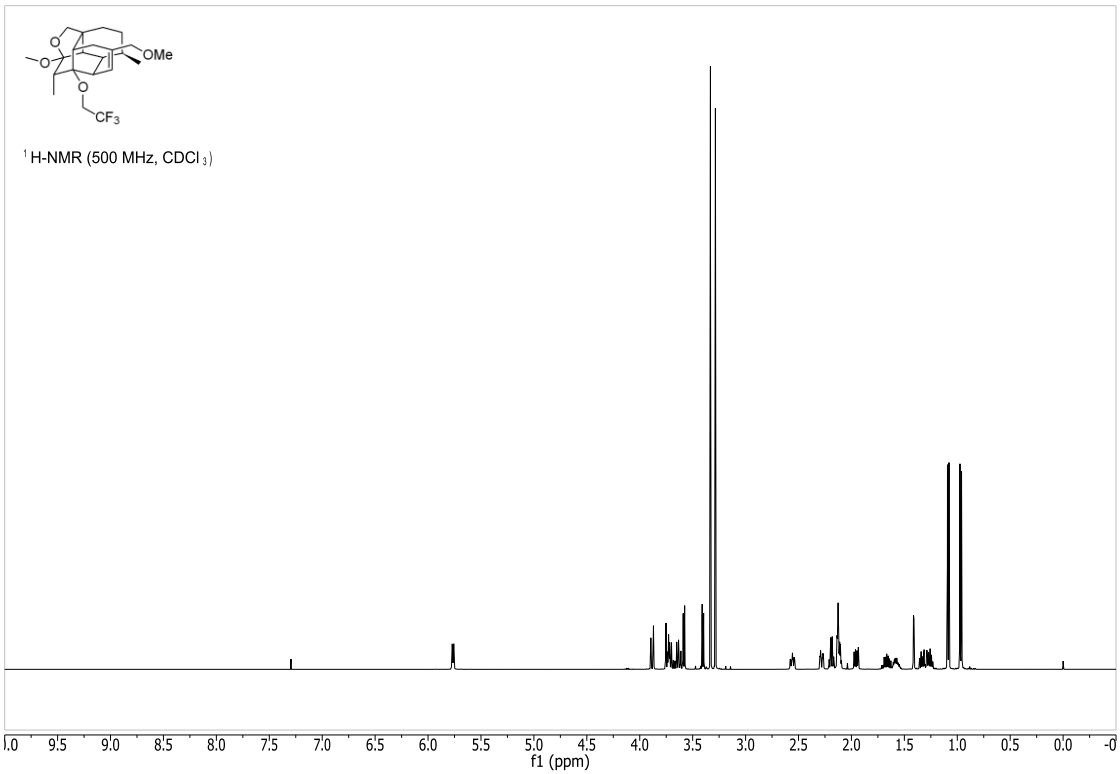
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CF3
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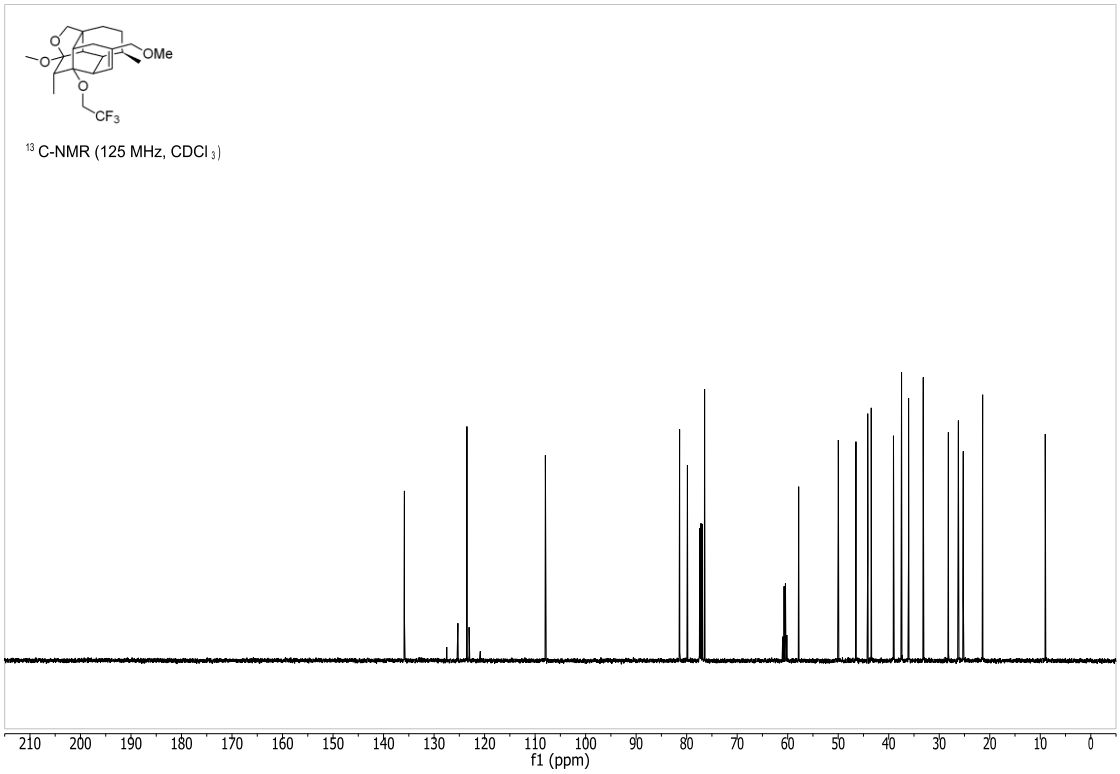
f1 (ppm)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CF3
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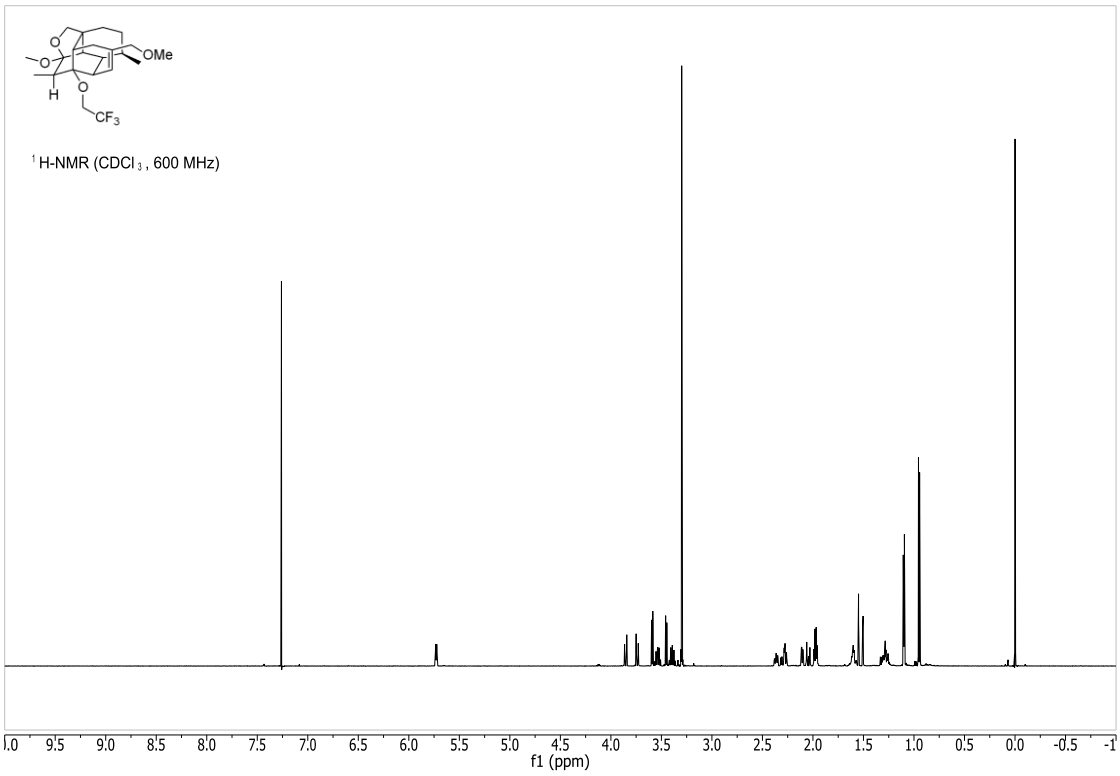
f1 (ppm)


OMe
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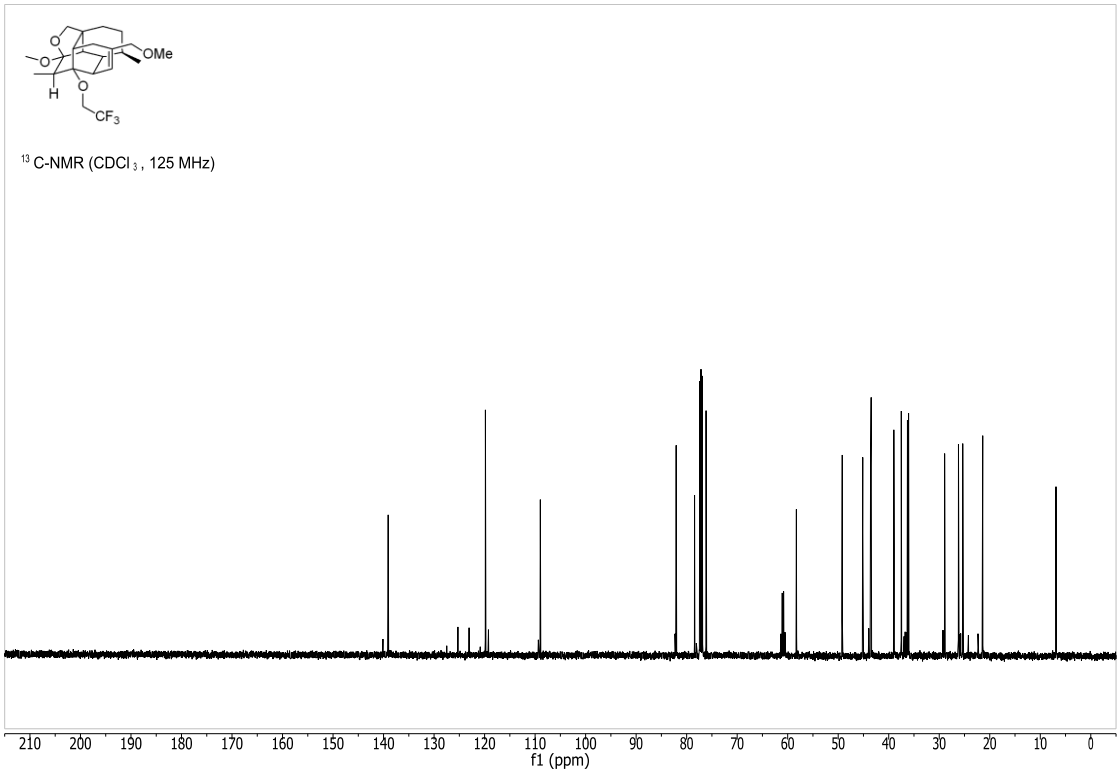
O
H
O
CF3
1H-NMR (CDCl3, 600 MHz)
f1 (ppm)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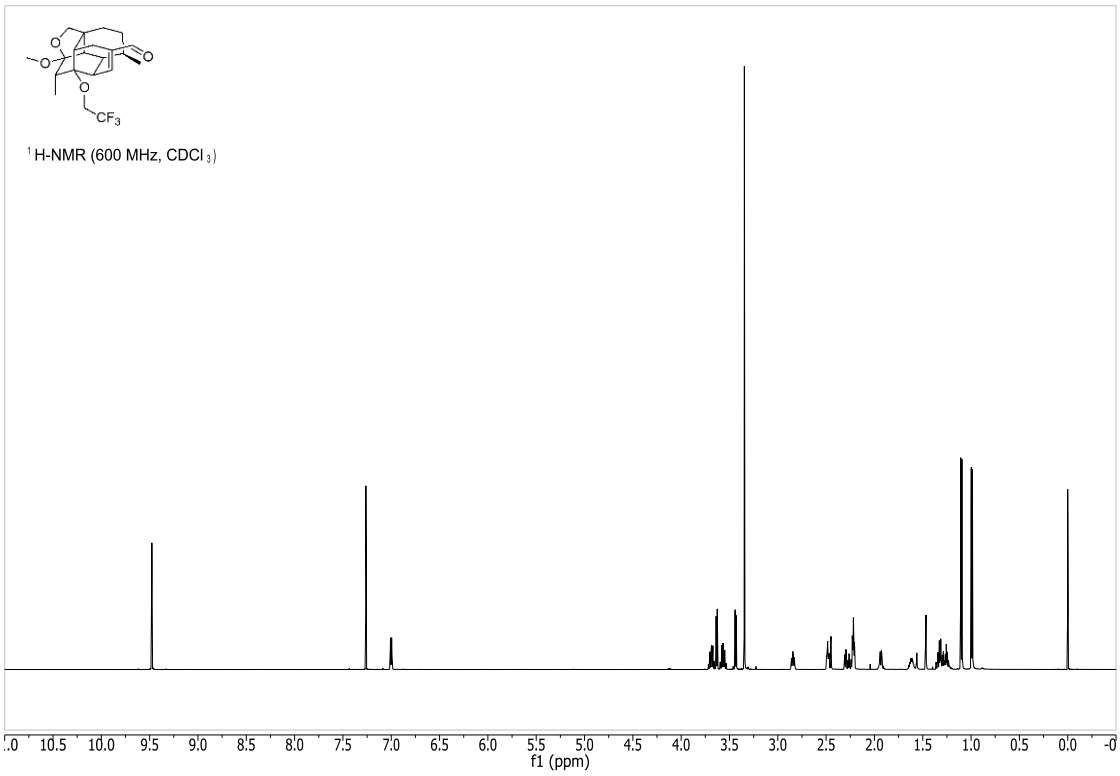
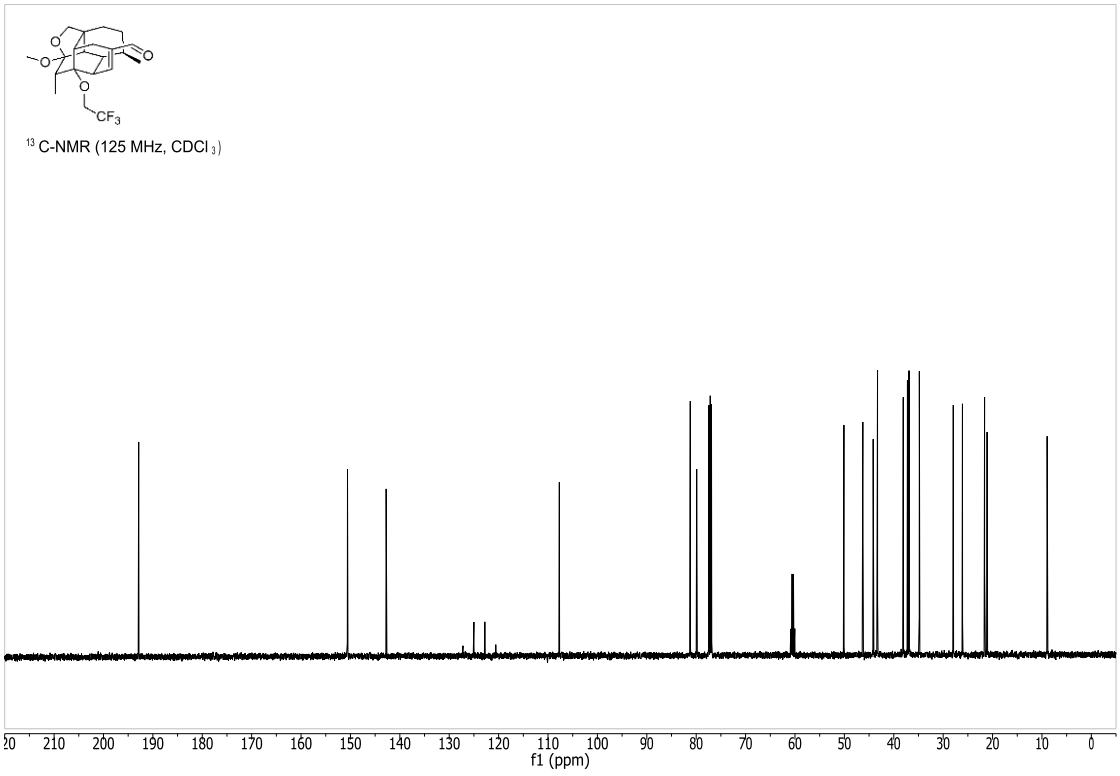
f1 (ppm)


^{1}H-NMR (600 MHz, CDCl$_3$)
f1 (ppm)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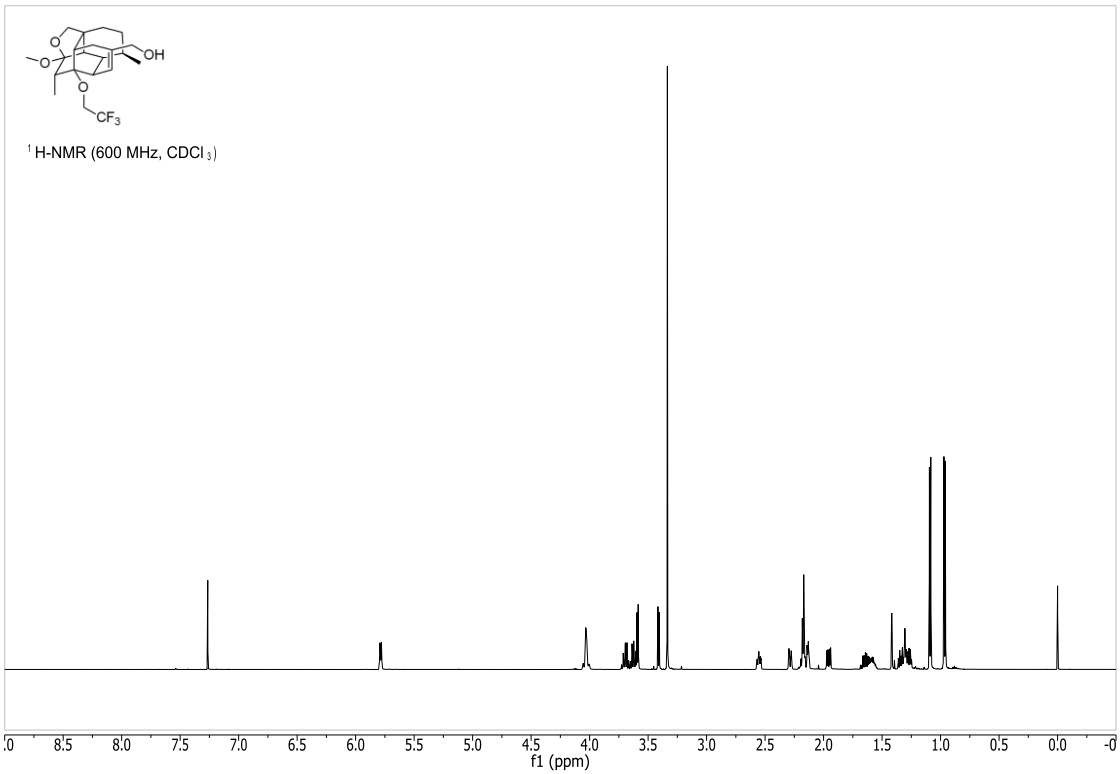
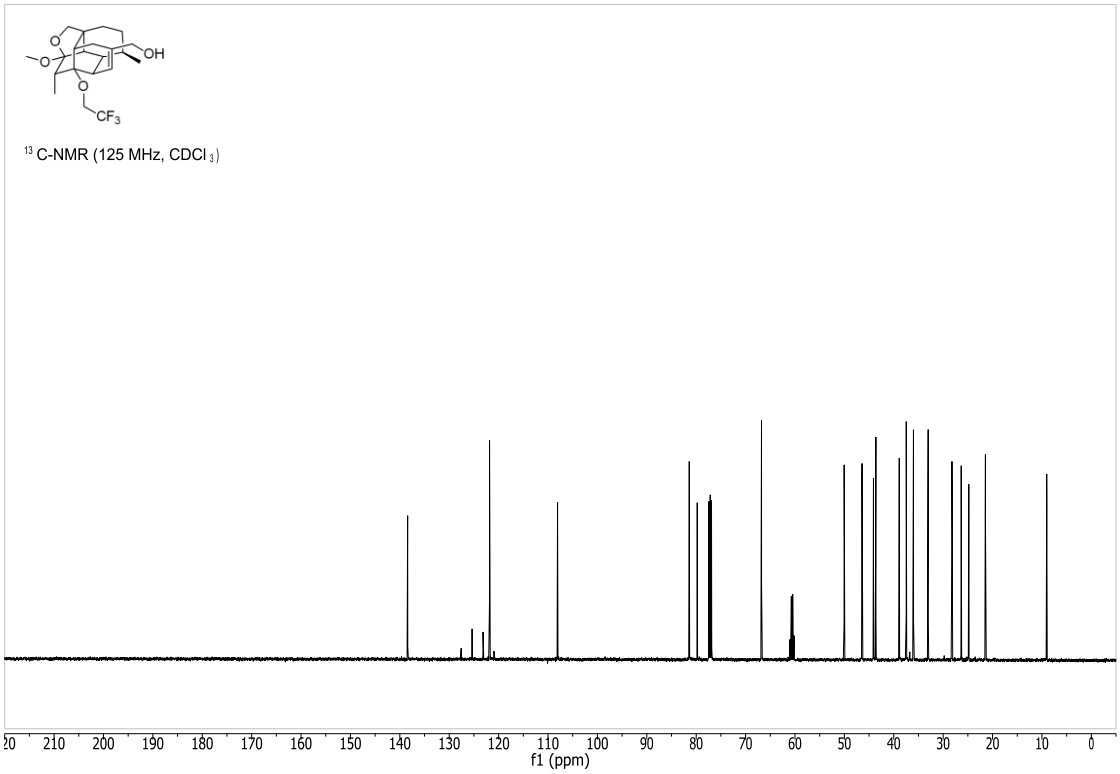
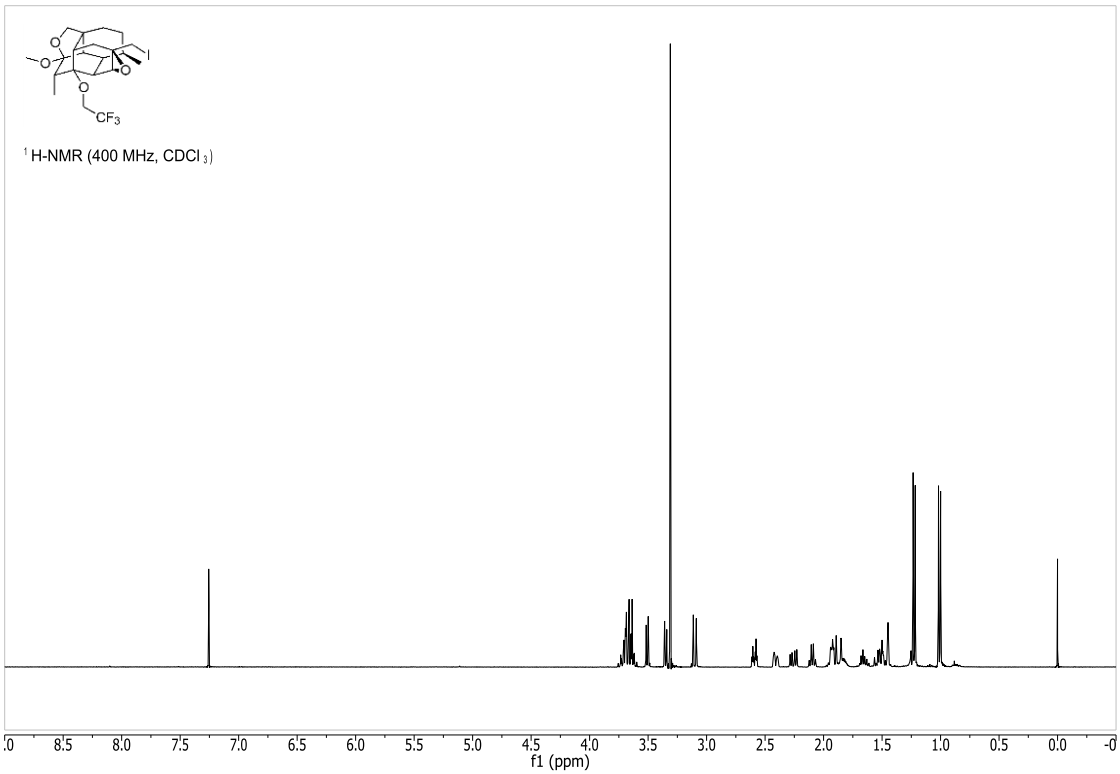
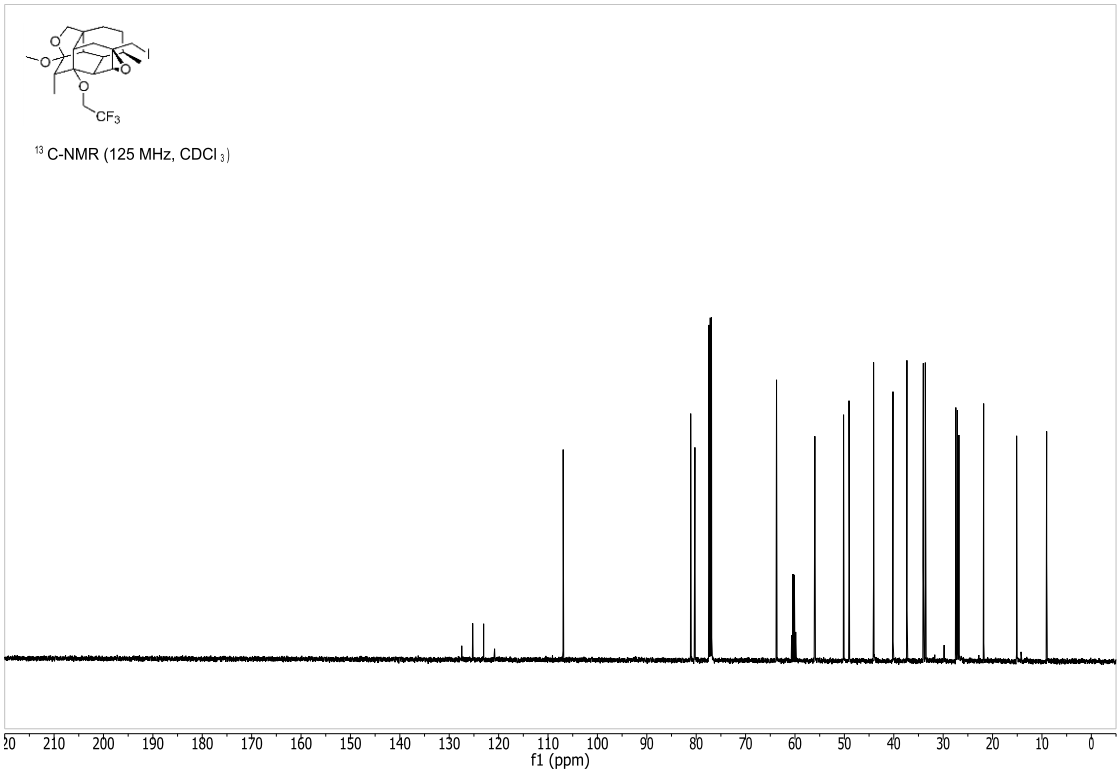
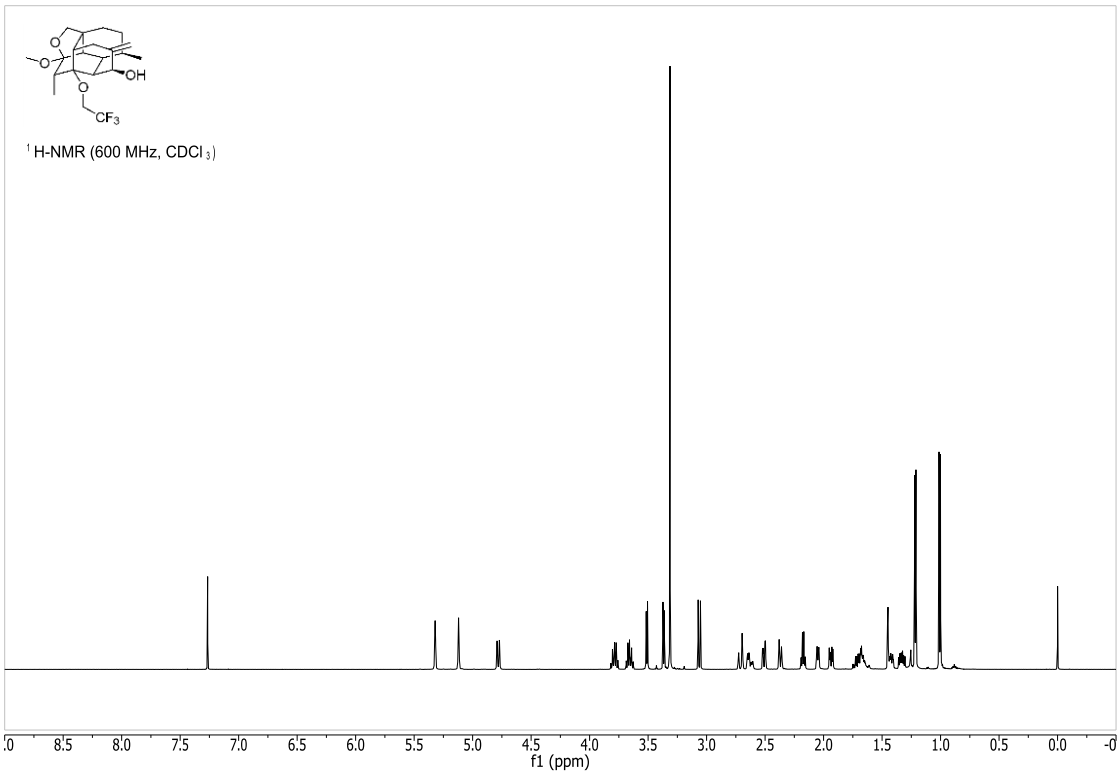
f1 (ppm)

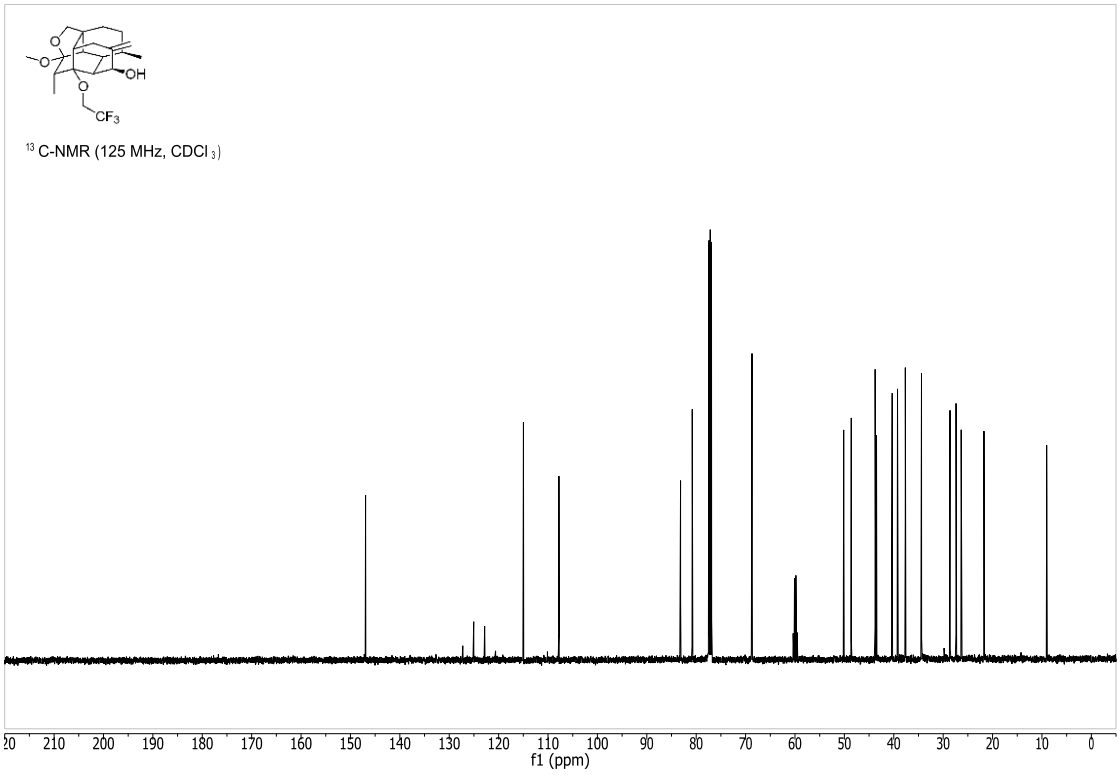

OH
O
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)


OH
O
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


O
O
I
O
CF3
1 H-NMR (400 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
O
I
O
CF3
13 C-NMR (125 MHz, CDCl 3)
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)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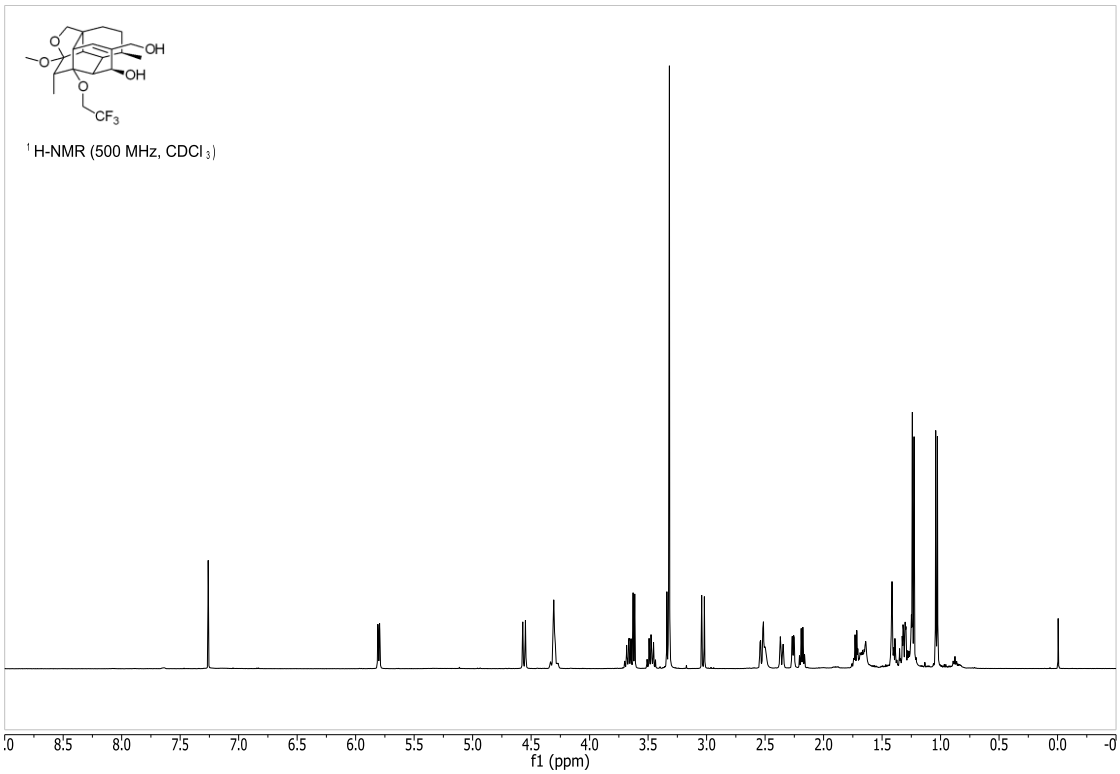
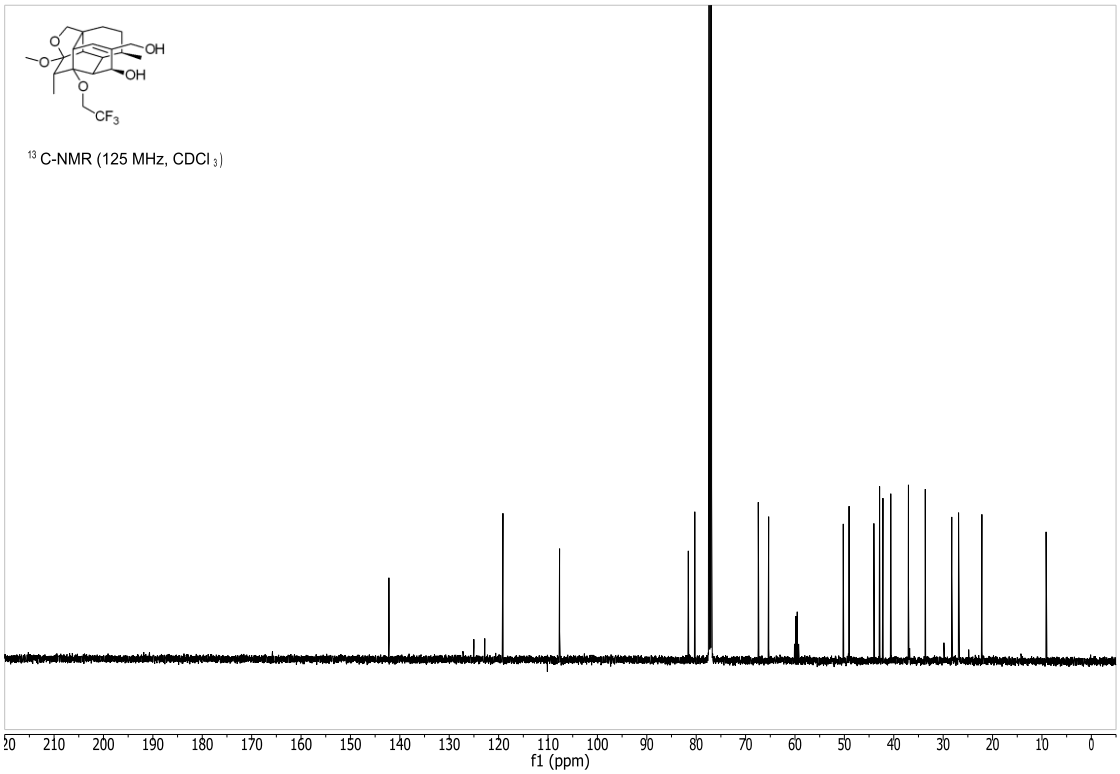
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


OH
OH
O
O
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)


OH
OH
O
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

References

(1) Shiao, M.-J.; Yang, C.-Y.; Lee, S.-H.; and Wu, T.-C. *Synth. Commun.* **1988**, 18, 359-366.

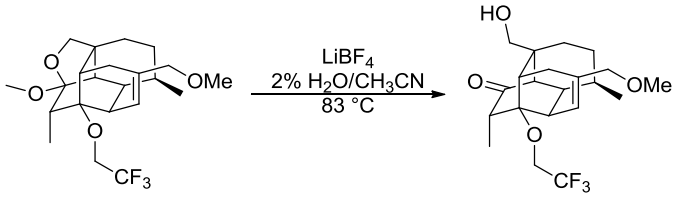
(2) Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025-1028.

(3) Wustenberg, B.; Pfaltz, A. *Adv. Synth. Catal.* **2008**, *350*, 174-178.

(4) Petter, R. C.; Banerjee, S.; Englard, S. *J. Org. Chem.* **1990**, 55, 3088-3097.

APPENDIX 3

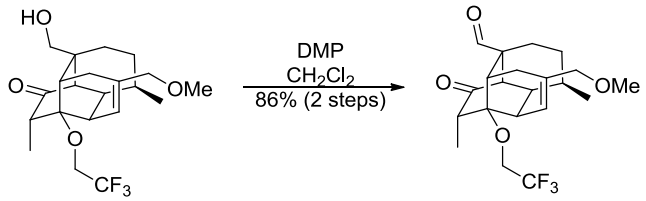
A3.1 Experimental Procedures for Chapter 4



4.5 **4.6**

A mixture of acetal (0.35 g, 0.841 mmol) and lithium tetrafluoroborate (0.39 g, 4.160 mmol) in 2% H_2O/CH_3CN (42 mL) was heated at 83 °C for 24 h. The reaction mixture was cooled to r.t., diluted with ethyl acetate (100 mL) and washed with saturated $NaHCO_3$ solution (3 × 30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated. The resultant solid was triturated with 15% ethyl acetate/hexanes to give a white solid (0.34 g), which was used without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (dt, *J* = 7.3, 1.6 Hz, 1H), 3.91 (d, *J* = 12.2 Hz, 1H), 3.79 (d, *J* = 12.2 Hz, 1H), 3.80 – 3.66 (m, 2H), 3.32 (s, 3H), 3.29 (d, *J* = 4.0 Hz, 2H), 2.71 (ddd, *J* = 10.7, 7.1, 3.1 Hz, 1H), 2.62 (q, *J* = 7.3 Hz, 1H), 2.35 (dt, *J* = 4.8, 3.3 Hz, 1H), 2.22 – 2.18 (m, 2H), 2.10 (ddd, *J* = 11.2, 3.7, 1.9 Hz, 1H), 1.94 – 1.77 (m, 3H), 1.68 (m, 2H), 1.34 (dt, *J* = 13.4, 6.8 Hz, 1H), 1.23 (ddd, *J* = 14.3, 12.2, 7.6 Hz, 1H), 1.16 (d, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.02, 136.75, 124.06 (q, *J* = 277.6 Hz), 122.65, 79.48, 76.42, 72.44, 60.94 (q, *J* = 34.6 Hz), 58.14, 56.97, 46.05, 40.63, 39.46, 35.76, 35.45, 34.17, 29.23, 26.14, 25.25, 21.32, 9.92; IR (film) 3425, 3390, 2943, 2914,

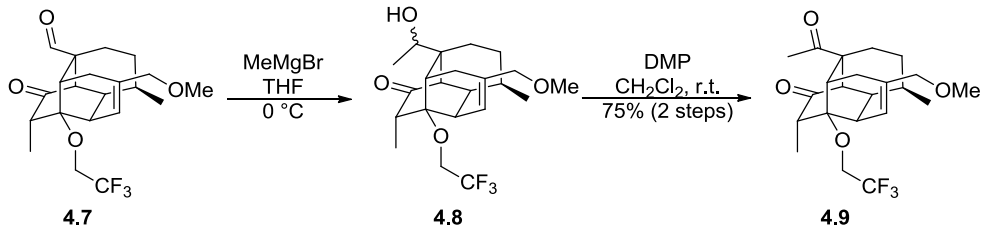
2873, 2812, 1705, 1278, 1153, 1105, 1074, 958, 906, 727, 617 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{30}F_3O_4$ $[M+H]^+$: 403.2091, found: 403.2089.



4.6 **4.7**

To a solution of alcohol (0.40 g, 0.99 mmol) in dichloromethane (50 mL), Dess-Martin periodinane (505.9 mg, 1.19 mmol) was added at r.t. in portions. After stirring for 2 h, the reaction mixture was diluted with ethyl acetate (100 mL), washed with a 1:1 mixture of saturated $NaHCO_3$ solution and 10% $Na_2S_2O_3$ solution (4 × 30 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (30% ethyl acetate/hexanes) to give a white solid (0.34 g, 86% over 2 steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.28 (s, 1H), 5.84 (dt, *J* = 7.1, 1.6 Hz, 1H), 3.90 (d, *J* = 12.2 Hz, 1H), 3.79 (d, *J* = 12.2 Hz, 1H), 3.79 (dq, *J* = 10.6, 8.3 Hz, 1H), 3.71 (dq, *J* = 10.6, 8.3 Hz, 1H), 3.32 (s, 3H), 2.94 (dd, *J* = 7.2, 3.2 Hz, 1H), 2.75 (ddd, *J* = 10.7, 7.1, 3.2 Hz, 1H), 2.33 (q, *J* = 7.3 Hz, 1H), 2.28 (dd, *J* = 19.5, 7.4 Hz, 1H), 2.21 (ddd, *J* = 11.1, 3.8, 2.1 Hz, 1H), 2.15 (d, *J* = 19.5 Hz, 1H), 2.10 (d, *J* = 2.1 Hz, 1H), 1.99 – 1.85 (m, 2H), 1.80 – 1.72 (m, 1H), 1.69 (ddd, *J* = 13.6, 12.1, 7.4 Hz, 1H), 1.49 (ddd, *J* = 13.3, 7.4, 6.0 Hz, 1H), 1.14 (d, *J* = 7.3 Hz, 3H), 1.13 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.03, 202.52, 136.57, 123.89 (d, *J* = 277.5 Hz), 122.02, 78.93, 76.15, 61.03 (q, *J* = 34.8 Hz), 58.31, 53.93, 50.22, 46.56, 38.30, 35.27, 34.49, 31.88, 26.79, 25.24, 24.87,

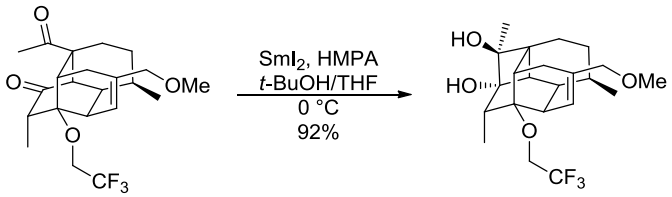
21.25, 9.73; IR (film) 2980, 2924, 2877, 2823, 1728, 1452, 1280, 1163, 1124, 1109, 966, 727 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{21}H_{28}F_3O_4$ $[M+H]^+$: 401.1934, found: 401.1934.



To a solution of aldehyde (7.3 mg, 0.0182 mmol) in THF (0.36 mL), methylmagnesium bromide (1.4 M in 3:1 THF/toluene, 0.06 mL, 0.084 mmol) was added dropwise at 0 °C. After stirring at 0 °C for 1.0 h, the reaction was quenched by saturated NH_4Cl solution (0.5 mL), diluted with water (1.0 mL) and extracted with ethyl acetate (3 × 1.5 mL). The extracts were combined, washed with brine (2.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to afford a colorless oil. ^{1}H-NMR analysis indicated a mixture of two diastereomers (dr 2:1). The crude product was used in the next step without further purification.

The crude product from the previous step was dissolved in dichloromethane (0.36 mL), to which Dess-Martin periodinane (11.6 mg, 0.0273 mmol) was added at r.t. After stirring for 2 h, the reaction mixture was diluted with ethyl acetate (5 mL), washed with a 1:1 mixture of saturated $NaHCO_3$ and 10% $Na_2S_2O_3$ (4 × 3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by prep-TLC (50% ethyl acetate/hexanes) to give a white solid (5.7 mg, 75% over 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.83 (d, *J* = 7.1 Hz,

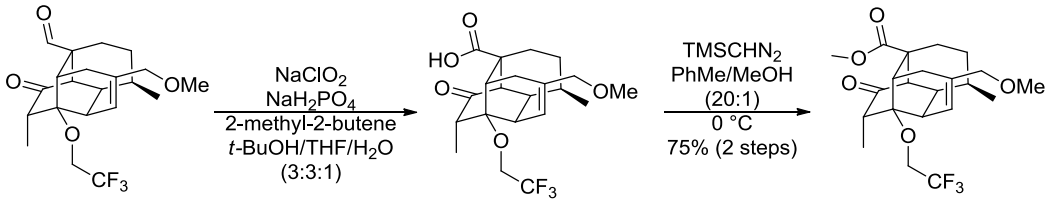
1H), 3.92 (d, *J* = 12.1 Hz, 1H), 3.80 (d, *J* = 12.1 Hz, 1H), 3.77 – 3.61 (m, 2H), 3.33 (s, 3H), 2.69 (ddd, *J* = 11.0, 7.0, 2.9 Hz, 1H), 2.55 (dt, *J* = 5.9, 2.6 Hz, 1H), 2.40 – 2.26 (m, 3H), 2.19 – 2.11 (m, 3H), 2.15 (s, 3H), 1.91 (qd, *J* = 12.9, 6.5 Hz, 1H), 1.73 (dtd, *J* = 13.0, 6.6, 3.6 Hz, 1H), 1.60 – 1.50 (m, 1H), 1.43 (dt, *J* = 13.8, 6.7 Hz, 1H), 1.15 (d, *J* = 7.2 Hz, 3H), 1.10 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.37, 210.36, 136.45, 123.89 (q, *J* = 278.8 Hz), 122.26, 79.42, 76.28, 61.17 (q, *J* = 34.5 Hz), 58.39, 54.82, 52.21, 46.72, 39.68, 35.51, 35.22, 33.88, 29.28, 26.03, 25.47, 24.97, 21.14, 9.58; IR (film) 2980, 2932, 2913, 2878, 1725, 1281, 1161, 1119, 965 cm^{-1} ; HRMS (ESI) *m/z* calcd. for $C_{22}H_{30}F_3O_4$ $[M+H]^+$: 415.2090, found: 415.2086.



4.9 **4.10**

Preparation of SmI_2/HMPA/THF solution (0.10 M): samarium filings (48.4 mg, 0.322 mmol) in a dry two-neck flask, sealed with a septum on one neck, were flame-dried, evacuated and back-filled with N_2 for three times. 1, 2-diiodoethane (45.3 mg, 0.161 mmol) in THF (1.6 mL) was added via syringe under N_2. The solution turned from light yellow to dark blue in a few seconds. After 2 h, HMPA (0.22 mL, 1.26 mmol) was added dropwise under N_2. The color of the solution changed quickly from dark blue to purple. After the mixture was stirred for 10 min., it was allowed to settle for 10 min before use.

Diketone (5.4 mg, 0.0130 mmol) was dissolved in *t*-BuOH/THF (1:20 v/v, 0.26 mL) and cooled to 0°C. N_2 was flushed for 10 min before SmI_2/HMPA/THF solution (0.10 M, 1.30 mL) was added dropwise. The purple reaction solution was stirred at 0 °C for 3.0 h before being opened to air and stirred vigorously for 1 min while the purple color faded away. The reaction was further quenched by 10% $Na_2S_2O_3$ (1 mL) and diluted with water (10 mL), extracted with ethyl acetate (3 × 5 mL). The extracts were combined and washed with brine (3 × 10 mL), dried over anhydrous Na_2SO_4 and concentrated. The crude product was purified by prep-TLC (60% ethyl acetate/hexanes) to give a white solid (5.0 mg, 92% yield). ^{1}H NMR (600 MHz, CD_3OD) δ 5.79 (d, *J* = 7.3 Hz, 1H), 3.93 – 3.83 (m, 2H), 3.82 – 3.70 (m, 2H), 3.29 (s, 3H), 3.20 (dd, *J* = 7.8, 3.2 Hz, 1H), 2.58 (ddd, *J* = 10.7, 7.2, 3.2 Hz, 1H), 2.52 (q, *J* = 7.1 Hz, 1H), 2.40 (dt, *J* = 10.9, 2.8 Hz, 1H), 2.13 (dd, *J* = 19.3, 7.8 Hz, 1H), 2.04 (d, *J* = 19.3 Hz, 1H), 1.74 (dd, *J* = 12.8, 5.7 Hz, 1H), 1.66 – 1.57 (m, 2H), 1.34 (s, 3H), 1.33 – 1.24 (m, 2H), 1.06 (d, *J* = 2.1 Hz, 1H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (CD_3OD, extracted from HSQC and HMBC) δ 133.99, 126.65, 125.79, 81.85, 80.67, 77.43, 77.30, 61.12, 57.70, 46.27, 44.21, 40.00, 39.88, 35.60, 34.08, 29.58, 28.55, 27.57, 26.28, 22.04, 18.73, 9.02; IR (film) 3345, 2935, 2910, 1277, 1150, 1112, 1027, 970 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{31}F_3NaO_4$ $[M+Na]^+$: 439.2066, found: 439.2068.

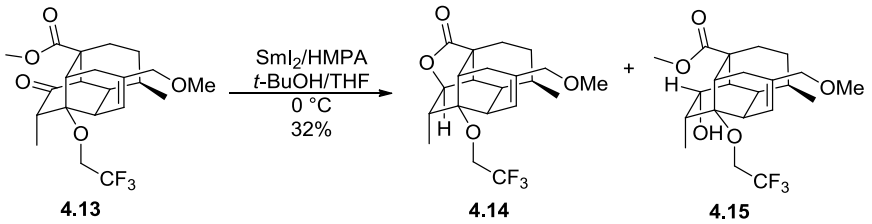


4.7 **4.12** **4.13**

To a mixture of aldehyde (6.0 mg, 0.0150 mmol) and sodium dihydrogen phosphate (6.4 mg, 0.0533 mmol) in *t*-BuOH/THF/H_2O (3:3:1 v/v/v, 0.5 mL) was added 2-methyl-2-butene (0.03 mL, 0.284 mmol), followed by sodium chlorite (5.6 mg, 0.0621 mmol). The reaction mixture was stirred at r.t. for 1.5 h then diluted with saturated NH_4Cl solution (1.0 mL), extracted with ethyl acetate (3 × 1.0 mL). The extracts were combined and washed with brine (2.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated to give a light yellow oil, which was used directly in the next step.

The crude product from the previous step was dissolved in toluene/methanol (20:1 v/v, 0.50 mL) then cooled to 0°C. Trimethylsilyldiazomethane (2.0 M in diethyl ether, 0.05 mL) was added dropwise. After stirring at 0 °C for 30 min., the reaction was concentrated and purified by column chromatography (30% ethyl acetate/hexanes) to give a white solid (4.8 mg, 75% yield for two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (d, *J* = 6.9 Hz, 1H), 3.91 (d, *J* = 12.4, 1H), 3.79 (d, *J* = 12.4 Hz, 1H), 3.76 – 3.65 (m, 2H), 3.68 (s, 3H), 3.32 (s, 3H), 2.70 (m, 2H), 2.51 (q, *J* = 7.2 Hz, 1H), 2.34 – 2.28 (m, 2H), 2.28 – 2.21 (m, 1H), 2.21 (d, *J* = 2.0 Hz, 1H), 2.12 (ddd, *J* = 11.2, 4.0, 2.2 Hz, 1H), 1.90 – 1.79 (m, 1H), 1.77 – 1.63 (m, 2H), 1.38 (dt, *J* = 13.7, 6.6 Hz, 1H), 1.17 (d, *J* = 7.2 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz,

$CDCl_3$) δ 212.37, 177.63, 136.56, 123.92 (q, J = 277.6 Hz), 121.99, 79.09, 76.18, 61.14 (q, J = 34.7 Hz), 58.31, 55.30, 52.84, 46.65, 46.38, 39.52, 37.28, 35.43, 33.70, 29.99, 25.98, 25.34, 21.15, 9.67; IR (film) 2979, 2926, 2878, 1729, 1454, 1436, 1281, 1250, 1161, 1120, 1103, 967 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{30}F_3O_5$ $[M+H]^+$: 431.2039, found: 431.2038.

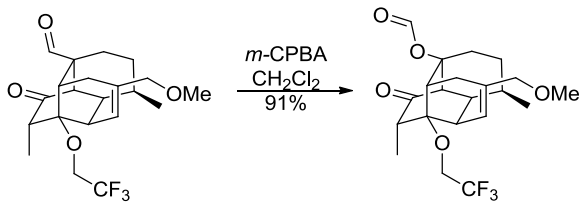


Ketoester (5.6 mg, 0.0130 mmol) was dissolved in *t*-BuOH/THF (1:20 v/v, 0.26 mL) and cooled to 0°C. N_2 was flushed for 10 min before SmI_2/HMPA/THF solution (0.10 M, 1.30 mL) was added dropwise. The purple reaction solution was stirred at 0 °C for 3.0 h before being opened to air and stirred vigorously for 1 min while the purple color faded away. The reaction was further quenched by 10% $Na_2S_2O_3$ (1 mL) and diluted with water (10 mL), extracted with ethyl acetate (3 × 5 mL). The extracts were combined and washed with brine (3 × 10 mL), dried over anhydrous Na_2SO4 and concentrated. The residue was purified by prep-TLC (60% ethyl acetate/hexanes) to give product **4.14** (higher R_f, white solid, 1.0 mg, 19% yield), **4.15** (lower R_f, colorless oil, 0.7 mg, 13% yield) and starting material (white solid, 2.0 mg, 36%).

Lactone **4.14**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (d, J = 7.2 Hz, 1H), 4.31 (d, J = 5.7 Hz, 1H), 3.88 (d, J = 12.2 Hz, 1H), 3.75 (d, J = 12.2 Hz, 1H), 3.70 (dq, J =

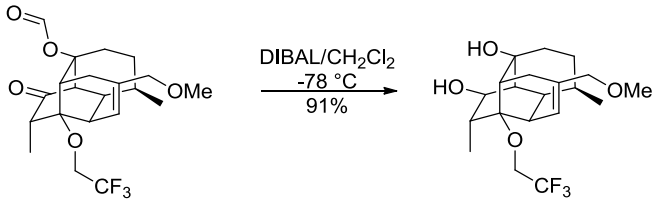
10.9, 8.4 Hz, 1H), 3.60 (dq, *J* = 10.9, 8.4 Hz, 1H), 3.30 (s, 3H), 2.60 (ddd, *J* = 10.6, 7.2, 2.9 Hz, 1H), 2.36 (dt, *J* = 11.3, 2.7 Hz, 1H), 2.25 – 2.11 (m, 5H), 1.85 (dd, *J* = 5.6, 2.2 Hz, 1H), 1.69 – 1.55 (m, 2H), 1.48 (m, 1H), 1.44 – 1.37 (m, 1H), 1.10 (d, *J* = 6.6 Hz, 3H), 1.05 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, extracted from HSQC and HMBC) δ 180.27, 135.14, 123.8, 122.12, 81.67, 78.27, 75.98, 60.79, 58.1, 44.9, 42.9, 37.42, 37.07, 36.34, 35.32, 32.54, 26.01, 25.72, 24.73, 21.13, 12.41; IR (film) 2981, 2925, 2851, 1766, 1283, 1163, 1152, 1112, 1099, 1024, 956, 858 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{28}F_3O_4$ $[M+H]^+$: 401.1934, found: 401.1935.

Alcohol **4.15**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.77 (d, *J* = 7.0 Hz, 1H), 4.02 (dt, *J* = 10.5, 3.1 Hz, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.75 (d, *J* = 12.2 Hz, 1H), 3.72 – 3.66 (m, 2H), 3.70 (s, 3H), 3.30 (s, 3H), 2.87 (dt, *J* = 4.8, 3.5 Hz, 1H), 2.60 (ddd, *J* = 10.7, 7.1, 3.2 Hz, 1H), 2.49 (ddd, *J* = 11.4, 3.8, 2.1 Hz, 1H), 2.19 – 2.11 (m, 3H), 2.02 – 1.97 (m, 1H), 1.88 – 1.76 (m, 2H), 1.74 – 1.63 (m, 2H), 1.44 – 1.40 (m, 1H), 1.35 – 1.27 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, extracted from HSQC and HMBC) δ 179.14, 135.8, 124.3, 123.51, 78.32, 76.61, 66.39, 60.58, 58.03, 52.38, 48.06, 45.36, 36.19, 35.38, 35.05, 34.85, 33.45, 32.25, 26.75, 25.33, 21.48, 7.59; IR (film) 3474, 2925, 1723, 1281, 1158, 1102, 1005, 863 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{31}F_3NaO_5$ $[M+Na]^+$: 455.2015, found: 455.2016.



4.7 **4.17**

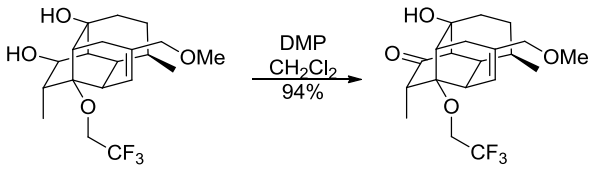
To a solution of aldehyde (150.0 mg, 0.374 mmol) in CH_2Cl_2 (7.5 mL), *meta*-chloroperoxybenzoic acid (70-75 wt%, with benzoic acid and water, 98.0 mg, 0.412 mmol) were added at r.t. in one portion. After stirring for 17 h, the reaction mixture was diluted with ethyl acetate (20 mL), washed with 10% $NaHSO_3$ solution (10 mL), saturated $NaHCO_3$ solution (3 × 10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (20% ethyl acetate/hexanes) to give a white foam (141.2 mg, 91% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (d, *J* = 0.9 Hz, 1H), 5.79 (ddd, *J* = 7.1, 2.0, 1.2 Hz, 1H), 3.91 (ddd, *J* = 12.4, 1.5, 0.7 Hz, 1H), 3.80 (ddd, *J* = 12.4, 1.5, 0.7 Hz, 1H), 3.73 – 3.63 (m, 2H), 3.33 (s, 3H), 3.04 – 2.97 (m, 1H), 2.82 – 2.69 (m, 2H), 2.52 – 2.47 (m, 1H), 2.49 (q, *J* = 7.3 Hz, 1H), 2.38 – 2.28 (m, 1H), 2.31 (d, *J* = 2.1 Hz, 1H), 2.27 – 2.18 (m, 1H), 1.95 – 1.70 (m, 2H), 1.59 – 1.41 (m, 2H), 1.20 (d, *J* = 7.3 Hz, 3H), 1.09 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.28, 159.77, 137.18, 123.67 (q, *J* = 277.8 Hz), 120.85, 85.02, 78.82, 75.69, 61.11 (q, *J* = 34.8 Hz), 58.61, 58.24, 46.65, 43.09, 39.14, 35.14, 33.49, 31.70, 27.02, 24.95, 20.30, 9.93; IR (film) 2980, 2929, 2877, 2823, 2249, 1712, 1452, 1375, 1282, 1165, 968, 867, 734 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{27}F_3NaO_5$ $[M+Na]^+$: 439.1703, found: 439.1706.



4.17 **4.18**

To a solution of keto-ester (488.4 mg, 1.17 mmol) in CH_2Cl_2 (10 mL) was added DIBAL (1.0 M in CH_2Cl_2, 3.51 mL) dropwise at -78 °C. The reaction was stirred at -78 °C for 2.0 h then quenched by 10% Rochelle's salt solution (20 mL). The mixture was diluted with ethyl acetate (40 mL), warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (60% ethyl acetate/hexanes) to give a white solid (415.7 mg, 91% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (d, *J* = 7.1 Hz, 1H), 3.86 (d, *J* = 12.2 Hz, 1H), 3.78 (br s, 1H), 3.74 (d, *J* = 12.2 Hz, 1H), 3.72 (dq, *J* = 10.8, 8.5 Hz, 1H), 3.64 (dq, *J* = 10.8, 8.5 Hz, 1H), 3.51 (s, 1H), 3.29 (s, 3H), 3.14 (br s, 1H), 2.47 (ddd, *J* = 10.8, 7.1, 3.1 Hz, 1H), 2.30 (dd, *J* = 7.4, 3.1 Hz, 1H), 2.25 (d, *J* = 18.9 Hz, 1H), 2.20 – 2.08 (m, 2H), 1.98 (tt, *J* = 7.2, 3.5 Hz, 1H), 1.94 (dt, *J* = 11.0, 2.7 Hz, 1H), 1.82 – 1.62 (m, 2H), 1.53 – 1.42 (m, 2H), 1.35 (dt, *J* = 13.5, 6.3 Hz, 1H), 1.09 (d, *J* = 7.2 Hz, 3H), 1.05 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.06, 124.15 (q, *J* = 277.6 Hz), 123.19, 79.79, 78.60, 78.32, 76.25, 60.69 (q, *J* = 34.5 Hz), 57.97, 48.17, 45.58, 42.56, 41.29, 37.51, 36.76, 32.77, 27.37, 24.79, 20.88, 15.16; IR (film) 3346, 2980, 2914, 2875, 1452, 1379, 1282, 1155, 1001, 966,

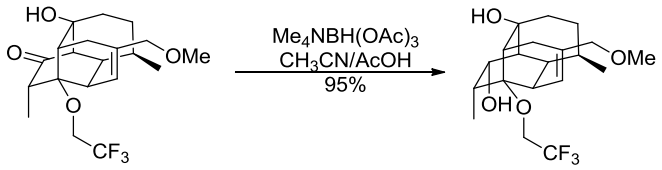
920, 854, 734 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{29}F_3NaO_4$ $[M+Na]^+$: 413.1910, found: 413.1916.



4.18 **4.19**

To a solution of diol (349.6 mg, 0.895 mmol) in water-saturated dichloromethane (18 mL), Dess-Martin periodinane (455.7 mg, 1.07 mmol) were added at r.t. in one portion. After stirring for 2 h, another portion of Dess-Martin periodinane (380 mg, 0.895 mmol) was added and the reaction was stirred for further 7 h. The reaction mixture was diluted with ethyl acetate (120 mL), washed with a 1:1 mixture of saturated $NaHCO_3$ solution and 10% $Na_2S_2O_3$ (4 × 30 mL) solution and brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was triturated with 50% ethyl acetate/hexanes and a white solid was collected by vacuum filtration. Purification of the filtrate by column chromatography (35% ethyl acetate/hexanes) gave another crop of white solid. Combined white solids weighed 326.8 mg (94% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.78 (d, *J* = 7.1 Hz, 1H), 3.91 (d, *J* = 12.3 Hz, 1H), 3.78 (d, *J* = 12.3 Hz, 1H), 3.71 (q, *J* = 8.4 Hz, 2H), 3.32 (s, 3H), 2.71 (ddd, *J* = 10.6, 7.1, 2.9 Hz, 1H), 2.53 (q, *J* = 7.4 Hz, 1H), 2.39 – 2.17 (m, 6H), 2.04 (d, *J* = 2.1 Hz, 1H), 1.87 – 1.64 (m, 2H), 1.52 – 1.38 (m, 2H), 1.16 (d, *J* = 7.3 Hz, 3H), 1.07 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.19, 136.66, 123.93 (d, *J* = 277.6 Hz), 122.16, 79.14, 76.08, 74.03, 61.89, 61.06 (q, *J* = 34.7 Hz), 58.17, 45.91, 43.56, 40.33, 37.03, 35.38, 33.65, 27.57, 24.83, 20.70, 9.79; IR

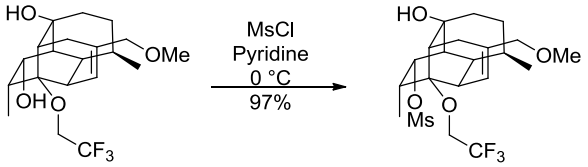
(film) 3396, 2981, 2927, 2879, 2825, 1712, 1456, 1280, 1161, 1120, 1020, 966, 920, 732 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{27}F_3NaO_4$ $[M+Na]^+$: 411.1754, found: 411.1756.



4.19 **4.20**

To a solution of keto-alcohol (173.4 mg, 0.446 mmol) in acetonitrile (5 mL) and acetic acid (10 mL), was added a suspension of tetramethylammonium triacetoxyborohydride (587.4 mg, 2.23 mmol) in acetonitrile (5 mL) at r.t. The reaction mixture was stirred for 3 h before it was quenched by saturated NH_4Cl solution (5 mL). After effervescence had ceased, the solution was diluted with water (10 mL) and ethyl acetate (30 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 20 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was triturated with hexanes and a white solid was collected by vacuum filtration. Purification of the filtrate by column chromatography (75% ethyl acetate/hexanes) gave another crop of white solid. The combined white solids weighed 165.4 mg (95% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.74 (dt, *J* = 7.0, 1.5 Hz, 1H), 4.58 (dd, *J* = 10.4, 3.2 Hz, 1H), 3.87 (d, *J* = 12.2 Hz, 1H), 3.74 (d, *J* = 12.2 Hz, 1H), 3.73 (dq, *J* = 10.8, 8.5 Hz, 1H), 3.61 (dq, *J* = 10.8, 8.5 Hz, 1H), 3.29 (s, 3H), 2.60 (ddd, *J* = 10.4, 7.0, 2.9 Hz, 1H), 2.55 – 2.47 (m, 1H), 2.33 (dq, *J* = 10.4, 7.3 Hz, 1H), 2.27 – 2.03 (m, 4H), 1.80 (m, 1H), 1.67 (m, 1H), 1.44 –

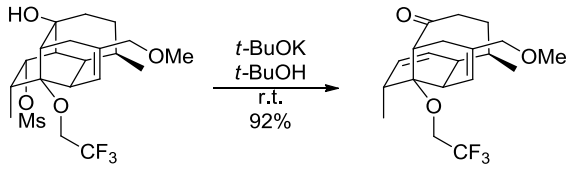
1.33 (m, 3H), 1.05 (d, J = 7.0 Hz, 3H), 1.01 (d, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.87, 124.23 (d, J = 277.8 Hz), 123.76, 79.02, 76.44, 74.78, 64.27, 60.58 (q, J = 34.3 Hz), 58.03, 51.29, 43.78, 38.46, 36.55, 36.45, 35.46, 33.52, 28.11, 24.82, 21.12, 7.74; IR (film) 3373, 2981, 2926, 2833, 1448, 1280, 1161, 1105, 1002, 966, 916, 864, 732 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{29}F_3NaO_4$ $[M+Na]^+$: 413.1910, found: 413.1909.



4.20 **4.21**

To a solution of diol (276.0 mg, 0.707 mmol) in anhydrous pyridine (12.0 mL), methanesulfonyl chloride (0.55 mL, 7.07 mmol) was added dropwise at 0 °C. The reaction was stirred at 0 °C for 15 h then quenched by 1 N HCl solution (10 mL) and diluted with ethyl acetate (200 mL). The mixture was washed with 1 N HCl solution (3 × 50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was triturated with 10% ethyl acetate/hexanes and a white solid was collected by vacuum filtration. Purification of the filtrate by column chromatography (60% ethyl acetate/hexanes) gave another crop of white solid. The combined white solids weighed 321.3 mg (97% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.73 (dt, J = 6.9, 1.5 Hz, 1H), 5.48 (dd, J = 10.6, 3.4 Hz, 1H), 3.86 (dd, J = 12.2, 1.1 Hz, 1H), 3.74 (dd, J = 12.2, 1.1 Hz, 1H), 3.72 (dq, J = 10.6, 8.4 Hz, 1H), 3.62 (dq, J = 10.6, 8.4 Hz, 1H), 3.29 (s, 3H), 3.05 (s, 3H), 2.62 (ddd, J = 10.6, 7.0, 2.9 Hz, 1H), 2.52 (dq, J = 11.0, 7.5 Hz, 1H), 2.47 (ddd, J = 11.4, 3.7, 2.1 Hz,

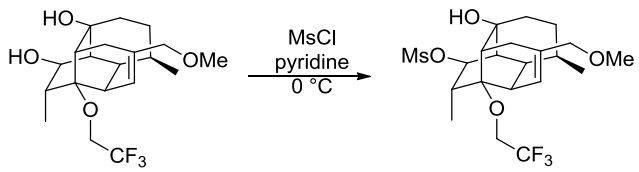
1H), 2.25 (d, J = 18.0 Hz, 1H), 2.20 (dd, J = 12.8, 6.3 Hz, 1H), 2.16 – 2.06 (m, 2H), 2.00 (s, 1H), 1.84 – 1.74 (m, 1H), 1.69 (m, 1H), 1.62 (dd, J = 3.4, 2.1 Hz, 1H), 1.47 – 1.34 (m, 2H), 1.06 (d, J = 7.0 Hz, 3H), 1.05 (d, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.13, 124.03 (d, J = 277.6 Hz), 122.96, 78.48, 77.01, 76.24, 74.28, 60.70 (q, J = 34.6 Hz), 58.13, 49.80, 43.53, 38.17, 38.01, 36.86, 36.09, 34.61, 33.23, 27.85, 24.70, 20.97, 8.91; IR (film) 3412, 2983, 2926, 1448, 1350, 1330, 1282, 1168, 1107, 966, 927, 918, 871, 732, 528 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{31}F_3NaO_6S$ $[M+Na]^+$: 491.1686, found: 491.1684.



4.21 **4.22**

To a solution of mesylate (220.8 mg, 0.471 mmol) in anhydrous *tert*-butanol (44 mL), potassium *tert*-butoxide (1.0 M in THF, 1.41 mL) was added dropwise at r.t. The solution became cloudy and turned yellow. After stirring for 1.5 h, the reaction was quenched by saturated NH_4Cl solution (10 mL) and diluted with ethyl acetate (50 mL) and water (50 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phases were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was triturated with hexanes and a white solid was collected by vacuum filtration. Purification of the filtrate by column chromatography (15% ethyl acetate/hexanes) gave another crop of white solid. The combined white solids weighed 161.4 mg (92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (dt, J = 5.7, 1.5 Hz, 1H),

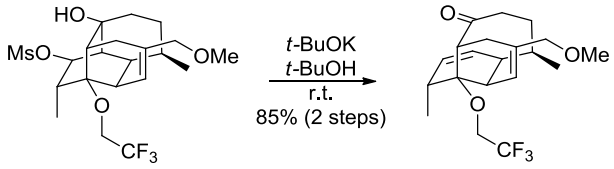
5.58 – 5.47 (m, 2H), 3.99 (d, *J* = 11.8, 1H), 3.85 (d, *J* = 11.8 Hz, 1H), 3.82 – 3.67 (m, 2H), 3.33 (s, 3H), 2.95 (d, *J* = 7.2 Hz, 1H), 2.83 – 2.78 (m, 1H), 2.74 (ddd, *J* = 14.9, 7.1, 4.0 Hz, 1H), 2.65 (qd, *J* = 7.0, 3.4 Hz, 1H), 2.60-2.53 (m, 1H), 2.46 – 2.38 (m, 1H), 2.25 (d, *J* = 18.6 Hz, 1H), 2.30-2.17 (m, 1H), 1.90 – 1.72 (m, 2H), 1.72 – 1.54 (m, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 1.04 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 211.79, 132.60, 131.32, 130.87, 125.45, 124.84 (d, *J* = 277.8 Hz), 78.93, 76.65, 60.91 (q, *J* = 33.8 Hz), 57.99, 54.19, 44.17, 38.23, 38.10, 37.56, 34.86, 29.76, 25.92, 23.46, 16.33; IR (film) 2927, 2875, 1676, 1280, 1155, 1105, 968, 856 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{28}F_3O_3$ $[M+H]^+$: 373.1985, found: 373.1983.



4.18 **4.23**

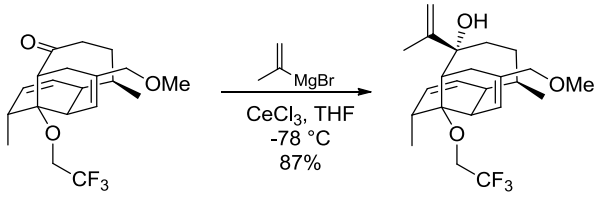
To a solution of diol (15.8 mg, 0.0404 mmol) in anhydrous pyridine (0.80 mL) methanesulfonyl chloride (0.03 mL, 0.404 mmol) was added dropwise at 0 °C. The reaction was stirred at 0 °C for 3 h then quenched by water (2 mL) and diluted with ethyl acetate (10 mL). The mixture was washed with 1 N HCl (5 × 2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (50% ethyl acetate/hexanes) to afford a white solid (18.9 mg, quantitative yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.71 (d, *J* = 7.2 Hz, 1H), 4.54 (dd, *J* = 4.6, 2.7 Hz, 1H), 3.86 (d, *J* = 12.3 Hz, 1H), 3.74 (d, *J* = 12.3 Hz, 1H), 3.67 (qd, *J* = 8.3, 2.5 Hz, 2H), 3.29 (s, 3H), 3.08 (s, 3H), 2.52 (ddd, *J* = 10.7, 7.1, 3.1 Hz, 1H), 2.34 (s, 1H), 2.32 – 2.20 (m, 3H), 2.19 – 2.12 (m, 2H), 2.09 –

1.97 (m, 1H), 1.84 – 1.74 (m, 2H), 1.69 (qd, J = 13.0, 6.3 Hz, 1H), 1.49 – 1.40 (m, 1H), 1.37 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.06 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.59, 123.96 (q, J = 277.7 Hz), 122.03, 88.47, 78.16, 76.58, 76.10, 60.97 (q, J = 34.5 Hz), 58.21, 47.81, 45.32, 41.82, 39.23, 39.07, 37.69, 36.72, 32.96, 27.47, 24.91, 20.80, 14.32; IR (film) 3529, 2925, 2876, 1456, 1333, 1281, 1170, 966, 935, 916, 845 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{21}H_{31}F_3NaO_6S$ $[M+Na]^+$: 491.1686, found: 491.1689.



4.23 **4.22**

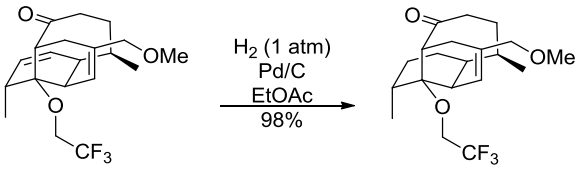
To a solution of mesylate (18.9 mg, 0.0404 mmol) in anhydrous *tert*-butanol (5.3 mL), potassium *tert*-butoxide (1.0 M in THF, 0.16 mL) was added dropwise at r.t. The reaction solution became cloudy and turned yellow. After stirring for 18 h, the reaction was quenched by saturated NH_4Cl (1 mL) and diluted with ethyl acetate (5 mL) and water (5 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (3 × 5 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. The crude product was purified by column chromatography (10% ethyl acetate/hexanes) to afford a white solid (12.8 mg, 85% yield over 2 steps).



4.22 **4.28**

Cerium (III) chloride heptahydrate[1] (58.8 mg, 0.158 mmol) was grounded to a fine powder and placed in a flask equipped with a stirring bar. The flask was heated slowly to 90 °C with evacuation and the powder was stirred at 90 °C for 3.5 h. The temperature was increased to 140 °C and maintained for 15 h. After the flask was cooled to r.t., nitrogen was introduced and THF (0.50 mL) was added. The resultant slurry was stirred vigorously under N_2 for 1 h and then cooled to -78°C. Isopropenylmagnesium bromide (0.5 M in THF, 0.26 mL) was added and after stirring for 1 h, ketone (9.8 mg, 0.0263 mmol) in THF (0.50 mL) was added. The reaction mixture was stirred at -78 °C for 8 h, and then warmed to r.t. naturally overnight. The reaction was quenched by saturated NH_4Cl solution (2 mL) at 0 °C and diluted with water (2 mL) and ethyl acetate (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to give a colorless oil (9.5 mg, 87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.79 (ddd, J = 9.8, 5.7, 2.5 Hz, 1H), 5.74 – 5.65 (m, 2H), 4.91 (p, J = 1.3 Hz, 1H), 4.88 (s, 1H), 3.85 (dt, J = 12.1, 1.3 Hz, 1H), 3.83 – 3.69 (m, 4H), 3.26 (s, 3H), 2.74 – 2.67 (m, 1H), 2.64 (m, 1H), 2.34 (m, 2H), 2.08 – 1.80 (m, 5H), 1.86 (d, J = 1.2 Hz, 3H), 1.57 (bs, 1H), 1.45 – 1.35 (m, 1H), 1.11 (d, J = 7.3 Hz, 3H), 1.10 (d, J = 7.4

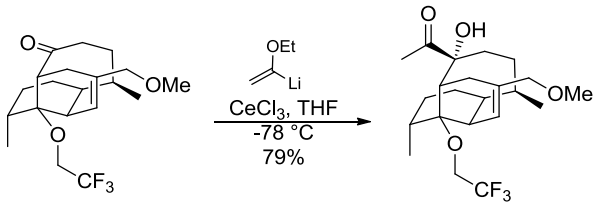
Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.94, 132.94, 132.77, 132.36, 124.53, 124.52 (d, *J* = 278.8 Hz), 112.18, 83.32, 79.34, 77.00, 61.21 (q, *J* = 33.7 Hz), 57.64, 45.21, 43.64, 37.43, 36.42, 35.75, 28.92, 27.27, 24.96, 22.50, 19.45, 16.69; IR (film) 3412, 2929, 2875, 1635, 1456, 1373, 1274, 1157, 1107, 972, 902, 850, 734 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{23}H_{33}F_3NaO_3$ $[M+Na]^+$: 437.2274, found: 437.2270.



4.22 **4.33**

To a solution of diene (247.3 mg, 0.664 mmol) in ethyl acetate (13.3 mL) was added palladium on carbon (10 wt%, 35.3 mg, 0.0332 mmol). The mixture was bubbled with H_2 for 5 min. then stirred at r.t. under H_2 balloon for 3.0 h. After that period of time the reaction mixture was filtered through a Celite pad and the filtrate was concentrated and then purified by column chromatography (15% ethyl acetate/hexanes) to give a colorless oil (243.6 mg, 98% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (ddd, *J* = 4.6, 2.4, 1.2 Hz, 1H), 3.97 (d, *J* = 11.9 Hz, 1H), 3.91 – 3.76 (m, 3H), 3.36 (s, 3H), 2.99 (dq, *J* = 5.9, 1.4 Hz, 1H), 2.73 (ddd, *J* = 12.1, 8.4, 3.9 Hz, 1H), 2.60 (q, *J* = 4.1 Hz, 1H), 2.44 (ddt, *J* = 18.2, 5.7, 2.7 Hz, 1H), 2.25 – 2.11 (m, 2H), 1.99 – 1.83 (m, 3H), 1.82 – 1.71 (m, 1H), 1.68 – 1.57 (m, 1H), 1.53 – 1.28 (m, 4H), 1.02 (d, *J* = 6.9 Hz, 3H), 0.94 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 215.76, 132.95, 127.03, 124.25 (q, *J* = 278.3 Hz), 78.93, 76.60, 61.98 (q, *J* = 34.0 Hz), 58.45, 54.04, 42.15, 38.83, 37.96, 37.44, 33.88, 31.44, 27.70, 27.09, 25.95, 24.03, 14.69; IR (film) 2933, 2873, 2821, 1674, 1454, 1377, 1280, 1153, 1103, 972, 850,

667, 536 cm^{-1}; HRMS (MALDI) *m/z* calcd. for $C_{20}H_{29}F_3O_3Li$ $[M+Li]^+$: 381.2224, found: 381.2235.



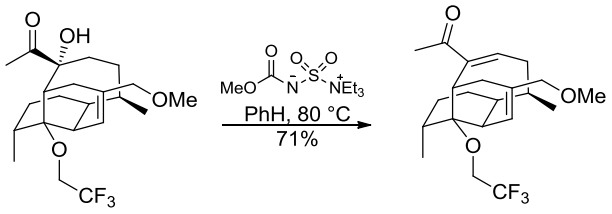
4.33 **4.34**

Cerium (III) chloride heptahydrate[1] (190 mg, 0.510 mmol) was grounded to a fine powder and placed in a flask equipped with a stir bar. The flask was heated slowly to 90 °C with evacuation and maintained at 90 °C for 3.5 h. After that period of time, the temperature was increased to 140 °C and the flask was heated at 140 °C for 15 h. The flask was then cooled to r.t., nitrogen was introduced and THF (2.5 mL) was added. The resultant slurry was stirred vigorously under N_2 for 2 h.

In a separate flask, *t*-BuLi (1.7 M in pentane, 1.5 mL, 2.5 mmol) was added dropwise to a solution of ethyl vinyl ether (0.57 mL, 6.0 mmol) in THF (3.0 mL) at -78 °C. The solution turned yellow and a precipitate formed. After the addition was completed, the cooling bath was removed and the mixture was allowed to warm to 0 °C over an ice-water bath and stirred at 0 °C for 15 min. while the yellow color was gradually discharged.

The resultant colorless 1-ethoxyvinyllithium solution (0.5 M, 0.80 mL) was added via syringe to the $CeCl_3$ suspension (cooled to -78 °C before the addition). A canary yellow mixture was formed and stirred for 1.0 h before ketone (45.0 mg, 0.134

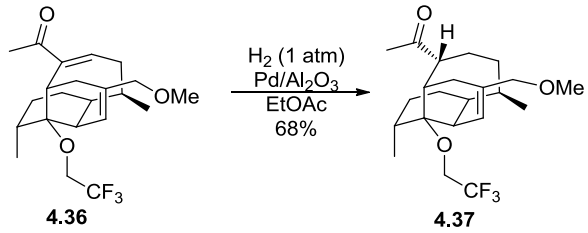
mmol) in THF (0.50 mL) was added. The reaction mixture was stirred at -78 °C for 45 min. and quenched by saturated NH_4Cl solution (3 mL) and extracted with ethyl acetate (5 × 6 mL). The combined organic layers were washed with brine (6 mL) and split into two portions; each was diluted with ethyl acetate to 50 mL and washed with cold 1N HCl solution (10 mL) and brine (5 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to give a colorless oil (44.3 mg, 79% yield). (Note: Prolonged exposure of the vinyl ether intermediate to acid during work-up could lead to its decomposition.) ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.71 (t, *J* = 3.2 Hz, 1H), 3.92 – 3.67 (m, 4H), 3.30 (s, 3H), 2.85 (ddt, *J* = 13.4, 11.4, 6.8 Hz, 1H), 2.64 (s, 1H), 2.57 (s, 1H), 2.37 (d, *J* = 8.1 Hz, 1H), 2.34 – 2.27 (m, 1H), 2.33 (s, 3H), 2.27 – 2.20 (m, 1H), 2.20 – 2.11 (m, 1H), 2.07 (ddt, *J* = 15.4, 7.5, 2.3 Hz, 1H), 1.97 (ddd, *J* = 15.6, 7.9, 2.2 Hz, 1H), 1.81 – 1.72 (m, 2H), 1.55 (d, *J* = 17.9 Hz, 1H), 1.48 – 1.36 (m, 3H), 1.32 – 1.23 (m, 1H), 1.08 (d, *J* = 7.4 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.45, 132.02, 126.42, 124.49 (q, *J* = 278.7 Hz), 82.45, 82.30, 76.80, 62.07 (q, *J* = 33.8 Hz), 58.20, 43.08, 41.02, 39.38, 36.82, 36.27, 30.63, 27.79, 25.82, 25.31, 24.71, 22.22, 22.19, 15.42; IR (film) 3441, 2931, 2872, 2825, 1703, 1456, 1377, 1357, 1280, 1157, 1107, 972, 910, 734 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{33}F_3O_4Li$ $[M+Li]^+$: 425.2485, found: 425.2486.



4.34 **4.36**

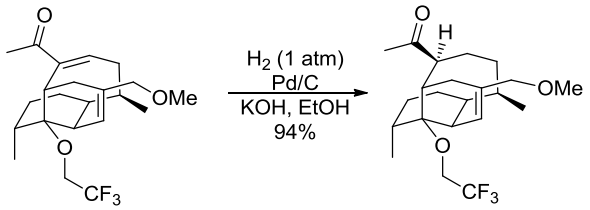
In a high-pressure tube, Burgess's reagent (37.8 mg, 0.159 mmol) was added to a solution of hydroxy ketone (33.2 mg, 0.0793 mmol) in benzene (8.0 mL) under N_2. The tube was then capped and heated at 80 °C for 1.0 h. The reaction solution turned from colorless to light yellow over time. After cooling to r.t. the reaction was concentrated, diluted with diethyl ether (30 mL) and washed with brine (3 × 10 mL). The aqueous phase was back-extracted with ether (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to afford a white solid (22.4 mg, 71% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.06 (t, *J* = 9.0 Hz, 1H), 5.72 (dt, *J* = 5.1, 1.6 Hz, 1H), 4.05 (d, *J* = 9.8 Hz, 1H), 3.97 – 3.79 (m, 3H), 3.77 (d, *J* = 12.1 Hz, 1H), 3,29 – 3.22 (m, 1H), 3.27 (s, 3H), 2.59 (t, *J* = 6.1 Hz, 1H), 2.46 (ddt, *J* = 19.1, 10.2, 2.4 Hz, 1H), 2.39 (s, 3H), 2.03 – 1.93 (m, 2H), 1.90 – 1.83 (m, 1H), 1.81 (d, *J* = 19.1 Hz, 1H), 1.72 (ddd, *J* = 13.0, 9.2, 2.6 Hz, 1H), 1.70 – 1.62 (m, 1H), 1.56 – 1.47 (m, 1H), 1.29 (dq, *J* = 13.7, 5.4 Hz, 1H), 1.14 (dtd, *J* = 13.7, 5.1, 2.4 Hz, 1H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.08, 146.73, 145.62, 136.10, 125.76, 124.58 (q, *J* = 278.2 Hz), 81.97, 76.71, 60.94 (q, *J* = 33.8 Hz), 57.70, 42.64, 41.24, 41.10, 33.22, 31.63, 31.52, 30.86, 28.51, 28.48, 27.79, 26.03, 15.43; IR (film) 2954, 2927, 2875, 1662, 1448, 1375, 1274, 1244, 1157,

1109, 968, 856 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{31}F_3O_3Na$ $[M+Na]^+$: 423.2118, found: 423.2113.



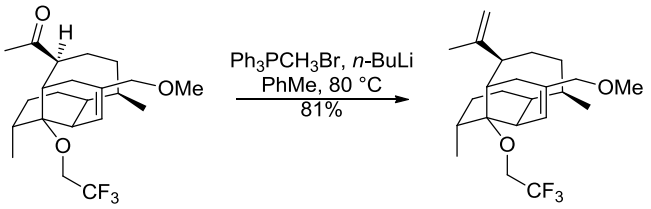
4.36 **4.37**

To a solution of α, β-unsaturated ketone (1.9 mg, 0.00474 mmol) in ethyl acetate (0.40 mL) was added palladium on activated alumina (10 wt%, 2.0 mg, 0.00188 mmol). The mixture was bubbled with H_2 for 5 min. then stirred at r.t. under H_2 balloon for 16 h. After that period of time the reaction mixture was filtered through a Celite pad, the filtrate was concentrated and purified by column chromatography (25% ethyl acetate/hexanes) to give a colorless oil (1.3 mg, 68% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.66 (s, 1H), 3.92 – 3.74 (m, 4H), 3.32 (s, 3H), 3.00 (dd, *J* = 7.4, 3.2 Hz, 1H), 2.73 – 2.63 (m, 1H), 2.51 (dt, *J* = 6.5, 3.2 Hz, 2H), 2.22 (s, 3H), 2.04 – 1.88 (m, 3H), 1.81 – 1.50 (m, 6H), 1.44 – 1.22 (m, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 1.00 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (C_6D_6, extracted from HSQC and HMBC) δ 208.61, 134.38, 125.63, 125.35, 82.38, 77.04, 62.48, 59.97, 58.18, 41.78, 39.07, 37.54, 37.05, 36.04, 32.83, 29.64, 28.23, 28.00, 27.63, 22.91, 20.82, 16.41; IR (film) 2927, 2874, 1706, 1462, 1279, 1157, 1105, 973, 857 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{33}F_3NaO_3$ $[M+Na]^+$: 425.2274, found: 425.2274.



4.36 **4.38**

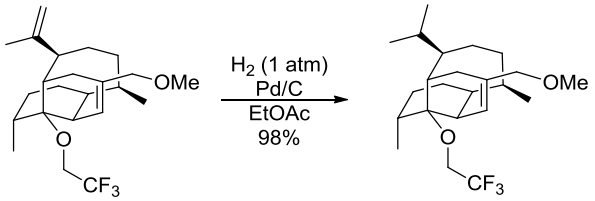
Enone (70.0 mg, 0.175 mmol) was dissolved in absolute ethanol (8.8 mL) containing potassium hydroxide (28.0 mg), to which palladium on carbon (10 wt%, 18.6 mg, 0.0175 mmol) was added. The mixture was bubbled with H_2 for 5 min. then stirred at r.t. under H_2 balloon for 27 h. The reaction was filtered through a Celite pad and the filter cake was washed with ethyl acetate. After brine (20 mL) was added to the filtrate, the mixture was extracted with ethyl acetate (3 × 15 mL). The combined extracts were dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to give a colorless oil (66.2 mg, 94% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.64 (m, 1H), 3.93 – 3.85 (m, 2H), 3.82 – 3.75 (m, 2H), 3.33 (s, 3H), 2.78 (d, *J* = 11.7 Hz, 1H), 2.44 (s, 1H), 2.35 (d, *J* = 6.8 Hz, 1H), 2.23 – 2.12 (m, 2H), 2.20 (s, 3H), 2.02 – 1.94 (m, 1H), 1.91 (d, *J* = 18.0 Hz, 1H), 1.68 – 1.43 (m, 6H), 1.34 (m, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 211.07, 133.68, 124.48 (q, *J* = 276.8 Hz), 124.66, 81.42, 76.14, 62.56 (q, *J* = 33.9 Hz), 58.34, 49.86, 42.62, 38.13, 37.23, 36.60, 33.29, 30.73, 29.16, 28.23, 26.88, 24.18, 24.04, 21.93, 14.53; IR (film) 2956, 2933, 2872, 2821, 1708, 1460, 1377, 1354, 1280, 1157, 1126, 1105, 972, 927, 850 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{33}F_3O_3Na$ $[M+Na]^+$: 425.2274, found: 425.2270.



4.38 **4.39**

In a high-pressure tube, *n*-BuLi (1.6 M in hexanes, 0.39 mL, 0.624 mmol) was added dropwise to a suspension of methyltriphenylphosphonium bromide (277.4 mg, 0.739 mmol) in toluene (3.5 mL) at 0 °C. The mixture turned to light yellow gradually. After stirring for 15 min., ketone (99.2 mg, 0.246 mmol) in toluene (1.0 mL) was added. The reaction tube was then sealed, warmed to r.t. and heated to 80 °C. After 20 h at 80 °C, the reaction was cooled to r.t., quenched by saturated NH_4Cl solution (5.0 mL), and extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was loaded on a silica gel plug and eluted with 5% ethyl acetate/hexanes. To remove the trace amount of triphenylphosphine, the eluate was concentrated, to which acetone (9.0 mL), sodium iodide (540 mg) and Merrifield resin (600 mg) were added. The resultant slurry was stirred at r.t. for 24 h then filtered through a Celite pad and washed with small amount of ethyl acetate. The filtrate was concentrated, re-dissolved in ethyl acetate, washed with water and brine and concentrated again. The residue was purified by column chromatography (5% ethyl ether/hexanes) to give a colorless oil (79.8 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.62 (m, 1H), 4.76 (t, J = 1.5 Hz, 1H), 4.62 (d, J = 1.3 Hz, 1H), 3.95 – 3.83 (m, 2H), 3.83 – 3.72 (m, 2H), 3.33 (s, 3H), 2.42 (s, 1H), 2.32 – 2.17 (m, 2H), 2.17 – 2.08 (m, 1H), 2.06 (d, J = 7.0 Hz, 1H), 2.03 – 1.89 (m, 2H), 1.83 – 1.78 (s, 3H), 1.62

(m, 1H), 1.56 – 1.28 (m, 8H), 0.99 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.22, 134.01, 124.63 (q, J = 278.4 Hz), 125.25, 110.04, 81.89, 76.65, 62.56 (q, J = 33.8 Hz), 58.25, 42.88, 42.02, 38.88, 38.39, 36.75, 32.99, 31.78, 28.34, 27.04, 25.98, 24.43, 24.21, 23.78, 14.58; IR (film) 2933, 2870, 1280, 1155, 1124, 1105, 1089, 974, 891 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{23}H_{35}F_3O_2Li$ $[M+Li]^+$: 407.2744, found: 407.2739.



4.39 **4.25**

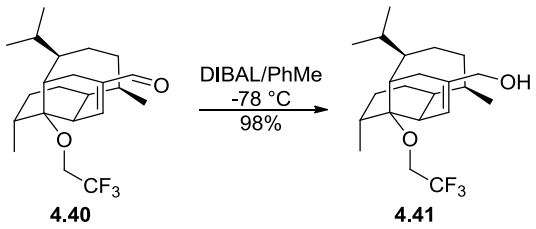
To a solution of diene (89.0 mg, 0.222 mmol) in ethyl acetate (2.2 mL) was added palladium on carbon (10 wt%, 23.6 mg, 0.0222 mmol). The mixture was bubbled with H_2 for 5 min. then stirred at r.t. for 36 h under H_2 balloon. After that period of time the reaction mixtures were filtered through a Celite pad and washed with ethyl acetate. The filtrate was concentrated to give a colorless oil (87.8 mg, 98% yield), which solidified in freezer to a white solid. (Note: The R_f of the product is as same as that of the starting material in ethyl acetate/hexanes solvent system, therefore the reaction was monitored by ^{1}H-NMR of aliquots.) ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.60 (m, 1H), 3.92 – 3.83 (m, 2H), 3.81 – 3.72 (m, 2H), 3.31 (s, 3H), 2.41 (m, 1H), 2.24 (m, 1H), 2.19 – 2.09 (m, 2H), 2.00 – 1.94 (m, 1H), 1.91 (d, J = 17.8 Hz, 1H), 1.75 – 1.63 (m, 1H), 1.54 – 1.25 (m, 9H), 1.25 – 1.14 (m, 1H), 0.96 (d, J = 6.8 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.88 (d, J = 6.6 Hz, 3H); ^{13}C

NMR (125 MHz, $CDCl_3$) δ 134.11, 124.72 (d, J = 278.5 Hz), 125.63, 82.09, 76.81, 62.38 (q, J = 33.7 Hz), 58.07, 42.62, 40.98, 38.21, 37.75, 37.48, 36.14, 33.12, 31.73, 28.85, 27.59, 25.47, 25.43, 24.44, 22.18, 20.94, 14.64; IR (film) 2956, 2933, 2872, 2819, 1463, 1456, 1375, 1280, 1155, 1122, 1101, 975, 850, 659 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{23}H_{37}F_3O_2Li$ $[M+Li]^+$: 409.2900, found: 409.2900.

4.25 **4.40**

In a high-pressure tube, a mixture of methylvinylether (18.0 mg, 0.0447 mmol), selenium dioxide (24.8 mg, 0.224 mmol) and benzene (1.0 mL) was heated at 80 °C for 60 h. The reaction was cooled to r.t., filtered through a Celite pad and washed with ethyl acetate. The filtrate was concentrated and purified by column chromatography (10% ethyl acetate/hexanes) to give a white solid (12.6 mg, 73% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.50 (s, 1H), 6.77 (m, 1H), 3.85 (dq, J = 10.8, 8.4 Hz, 1H), 3.75 (dq, J = 10.8, 8.4 Hz, 1H), 2.70 (m, 1H), 2.40 (d, J = 17.8 Hz, 1H), 2.35 – 2.24 (m, 2H), 2.21 (ddp, J = 13.8, 6.9, 3.7 Hz, 1H), 2.06 (dtt, J = 12.2, 6.0, 2.9 Hz, 1H), 1.75 (td, J = 9.2, 4.4 Hz, 1H), 1.63 –1.32 (m, 10H), 0.99 (d, J = 6.9 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.65, 152.46, 139.88, 124.19 (q, J = 278.7 Hz), 82.21, 62.01 (q, J = 34.0 Hz), 43.28, 40.84, 40.18, 37.26, 36.71, 35.88, 33.00, 32.19, 28.60, 27.55, 25.30, 24.19, 22.13, 20.92, 20.61, 14.68; IR (film) 2956, 2933, 2872, 1681, 1649,

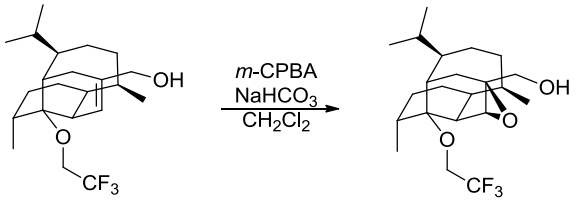
1278, 1157, 1118, 972 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{33}F_3O_2Li$ $[M+Li]^+$: 393.2587, found: 393.2581.



4.40 **4.41**

To a solution of aldehyde (53.3 mg, 0.138 mmol) in toluene (10 mL) was added DIBAL (1.0 M in toluene, 0.21 mL) dropwise at -78 °C. The reaction was stirred at -78 °C for 1.5 h then quenched by 10% Rochelle's salt solution (5 mL). The mixture was diluted with ethyl acetate (5 mL), warmed to r.t. and stirred vigorously until two clear layers formed. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10% ethyl acetate/hexanes) to give a colorless oil (52.5 mg, 98% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.62 (m, 1H), 4.06 (q, *J* = 13.1 Hz, 2H), 3.86 (dq, *J* = 10.7, 8.6 Hz, 1H), 3.76 (dq, *J* = 10.7, 8.6 Hz, 1H), 2.46 – 2.37 (m, 1H), 2.29 (ddt, *J* = 17.8, 6.5, 2.9 Hz, 1H), 2.21 – 2.09 (m, 2H), 2.03 – 1.90 (m, 2H), 1.76 – 1.62 (m, 1H), 1.62 – 1.15 (m, 11H), 0.96 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.37, 124.72 (d, *J* = 278.6 Hz), 124.29, 82.12, 67.15, 62.31 (q, *J* = 33.7 Hz), 42.62, 40.86, 38.06, 37.71, 37.49, 36.19, 33.11, 31.77, 28.83, 27.58, 25.52, 25.16, 24.47, 22.14, 20.90, 14.66; IR (film) 3342, 2956, 2933, 2872,

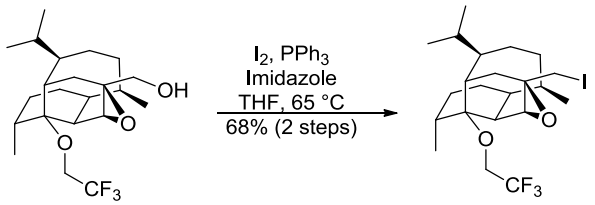
2358, 2341, 1466, 1278, 1155, 1124, 975, 734 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{35}F_3O_2Li$ $[M+Li]^+$: 395.2744, found: 395.2730.



4.41 **4.42**

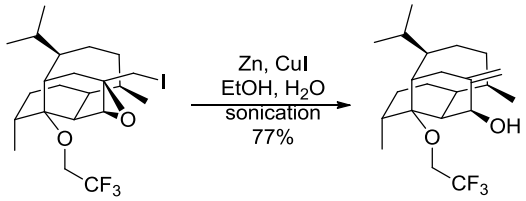
A mixture of allylic alcohol (40.0 mg, 0.103 mmol) and $NaHCO_3$ (43.3 mg, 0.515 mmol) in CH_2Cl_2 (2.0 mL) was cooled to 0 °C, to which *meta*-chloroperoxybenzoic acid (70-75 wt%, with benzonic acid and water, 36.8 mg, 0.154 mmol) was added in one portion. The mixture was allowed to warm to r.t. naturally and stirred for total 18 h. After water (2 mL) and ethyl acetate (10 mL) were added to the mixture, the organic phase was separated and washed with saturated $NaHSO_3$ solution (3 × 2 mL), saturated $NaHCO_3$ solution (3 × 2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The resultant solid (43.4 mg) was used in the next step without further purification. An analytical sample was obtained by triturating the solid with hexanes. ^1H NMR (600 MHz, $CDCl_3$) δ 4.19 (m, 1H), 3.81 – 3.70 (m, 2H), 3.65 (dd, *J* = 12.3, 9.7 Hz, 1H), 3.38 (s, 1H), 2.69 (d, *J* = 3.9 Hz, 1H), 2.26 (dd, *J* = 15.8, 8.0 Hz, 1H), 2.14 (dqd, *J* = 13.7, 7.2, 3.9 Hz, 1H), 2.09 – 1.99 (m, 1H), 1.97 (d, *J* = 8.0 Hz, 1H), 1.75 (d, *J* = 9.2 Hz, 1H), 1.69 (td, *J* = 9.8, 4.0 Hz, 1H), 1.63 – 1.43 (m, 7H), 1.43 – 1.23 (m, 4H), 0.95 – 0.89 (m, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 124.75 (q, *J* = 278.3 Hz), 80.78, 62.59, 61.89 (q, *J* = 33.6 Hz), 60.63, 59.00, 42.25, 40.77, 37.44, 36.90, 35.35, 34.74, 33.23, 29.93, 28.78, 28.29, 26.37, 24.59,

23.25, 21.87, 21.16, 14.23; IR (film) 3431, 2954, 2937, 2873, 1456, 1278, 1155, 1122, 974 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{35}F_3O_3Li$ $[M+Li]^+$: 411.2693, found: 411.2693.



4.42 **4.43**

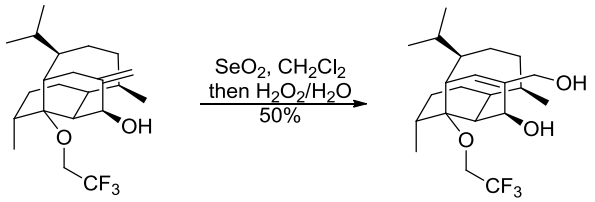
In a high-pressure tube, a mixture of triphenylphosphine (32.6 mg, 0.124 mmol), imidazole (11.2 mg, 0.165 mmol), iodine (31.5 mg, 0.124 mmol) and alcohol (33.5 mg, 0.0828 mmol) in THF (1.5 mL) was heated to 65 °C and stirred for 5.0 h. The reaction was cooled to r.t., diluted with ethyl acetate (5 mL), washed with 10% $Na_2S_2O_3$ solution (2 × 3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated on rotovap. The residue was loaded on a silica gel column and eluted with 5% diethyl ether/hexanes. The eluate was collected, concentrated on rotovap and placed under high vacuum briefly to give a white solid (27.8 mg, 68% for two steps). The product was used immediately afterward. (Note: This product was unstable when concentrated; partial decomposition was observed after it was dried under high vacuum overnight at room temperature.)



4.43 **4.44**

Commercial zinc powder was stirred with 1 N HCl solution for 5 min, and then the acid solution was removed by a pipette. The zinc residue was washed with water (3 ×), absolute ethanol (3 ×) and dry diethyl ether (3 ×). (The wash solutions were removed each time by a pipette.) The material was then dried under high vacuum overnight. The pre-treated zinc powder (73.4 mg, 1.12 mmol) and copper(I) iodide (106.6 mg, 0.560 mmol) are sonicated under N_2 in aqueous ethanol (4.5 ml, 40% H_2O, v/v) for 5 min. A mixture of iodide (28.8 mg, 0.0560 mmol) in ethanol (2.0 ml) was added to the resultant black suspension and the sonication was continued for 1.5 h. The reaction was quenched by saturated NH_4Cl solution (1.0 mL), filtered through a Celite pad and washed with diethyl ether. The filtrate was extracted with ether (3 × 5 mL), and the combined extracts were washed with brine (5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (10% diethyl ether/hexanes) to give a colorless oil (16.7 mg, 77%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.09 (s, 1H), 5.03 (s, 1H), 4.26 (d, *J* = 7.9 Hz, 1H), 4.05 (dq, *J* = 10.3, 8.3 Hz, 1H), 3.81 (dq, *J* = 10.3, 8.3 Hz, 1H), 2.75 (d, *J* = 7.8 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.41 (d, *J* = 4.8 Hz, 1H), 2.31 (d, *J* = 16.2 Hz, 1H), 2.16 (pd, *J* = 7.1, 4.1 Hz, 1H), 2.06 (d, *J* = 7.6 Hz, 1H), 1.93 (dq, *J* = 13.6, 7.0 Hz, 1H), 1.84 (dtd, *J* = 14.0, 6.8, 4.3 Hz, 1H), 1.78 (m, 1H), 1.71 (m, 1H), 1.68 – 1.46 (m, 4H), 1.46 – 1.21 (m, 4H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.97 – 0.91 (m, 9H); ^{13}C NMR (126 MHz,

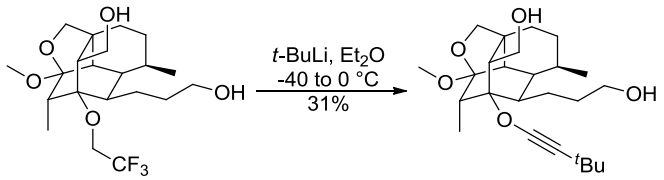
$CDCl_3$) δ 148.36, 124.50 (q, *J* = 277.9 Hz), 113.11, 84.37, 75.62, 60.78 (q, *J* = 33.8 Hz), 47.92, 44.98, 40.61, 38.69, 36.02, 36.00, 33.35, 31.23, 29.04, 28.89, 28.56, 26.67, 25.36, 21.66, 20.76, 15.87; IR (film) 3417, 2954, 2931, 2875, 1454, 1393, 1276, 1159, 1118, 972, 906, 879, 734 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{35}F_3O_2Li$ $[M+Li]^+$: 395.2744, found: 395.2734.



4.44 **4.46**

A mixture of olefin (12.0 mg, 0.0309 mmol) and selenium dioxide (17.1 mg, 0.154 mmol) in CH_2Cl_2 (3.0 mL) was stirred at r.t. for 6 h then hydrogen peroxide (30 wt% in water, 0.035 mL, 0.309 mmol) was added and stirred for 16 h. The reaction was diluted with ethyl acetate (6 mL) and washed with 10% $NaHSO_3$ solution (2 mL), saturated $NaHCO_3$ solution (2 mL) and brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (15% ethyl acetate/hexanes) to give a colorless oil (6.3 mg, 50% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.72 (d, *J* = 5.8 Hz, 1H), 4.34 – 4.16 (m, 2H), 4.06 (d, *J* = 11.1 Hz, 1H), 3.71 – 3.52 (m, 2H), 2.84 (d, *J* = 11.2 Hz, 1H), 2.60 (s, 1H), 2.40 (d, *J* = 4.6 Hz, 1H), 2.27 (d, *J* = 5.7 Hz, 1H), 2.22 – 2.07 (m, 2H), 2.06 – 1.96 (m, 1H), 1.88 (ddt, *J* = 25.5, 12.9, 4.8 Hz, 2H), 1.66 (pd, *J* = 6.8, 3.9 Hz, 1H), 1.60 – 1.49 (m, 1H), 1.49 – 1.31 (m, 4H), 1.31 – 1.12 (m, 2H), 1.10 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.93, 124.47,

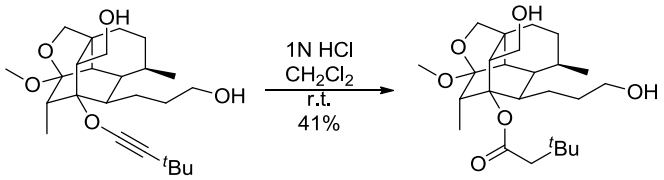
124.38 (q, J = 278.3 Hz), 83.60, 72.61, 66.83, 59.81 (q, J = 33.8 Hz), 50.87, 45.86, 40.27, 37.64, 35.85, 33.80, 33.28, 30.63, 29.82, 28.91, 28.46, 26.52, 21.14, 19.73, 17.54; IR (film) 3429, 2953, 2927, 2358, 2345, 1269, 1161, 1111, 1006, 974, 894 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{22}H_{35}F_3O_3Li$ $[M+Li]^+$: 411.2693, found: 411.2682.



4.54 **4.55**

To a mixture of diol (50.0 mg, 0.118 mmol) in diethyl ether (5.0 mL) cooled to -40 °C, was added *tert*-butyllithium (1.7 M in pentane, 1.0 mL) dropwise. After the addition was completed, the reaction mixture was allowed to warm up to 0 °C naturally (over 2.0 h). The reaction was stirred at 0 °C for further 30 min. then quenched with methanol (0.5 mL) and saturated NH_4Cl solution (1.0 mL). The mixture was extracted with ethyl acetate (3 × 2 mL) and the combined extracts were washed with brine (2 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. ^{1}H-NMR analysis of the crude product indicated 50% conversion of starting material to product. The crude product was re-subjected to the same reaction conditions and ^{1}H-NMR analysis indicated complete consumption of the starting material. The crude product was purified by column chromatography (40% ethyl acetate/hexanes) to afford a white solid (15.4 mg, 31% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.07 (dd, J = 11.0, 3.6 Hz, 1H), 3.95 – 3.85 (m, 1H), 3.65 (d, J = 6.7 Hz, 1H), 3.60 (m, 2H), 3.39 (d, J = 6.7 Hz, 1H), 3.31 (s, 3H), 2.56 (q, J = 7.2 Hz, 1H), 2.32 (dt, J = 9.4, 2.7 Hz, 1H), 2.29 – 2.24 (m, 1H), 2.22 (dt, J = 11.8, 2.7 Hz, 1H), 2.07 – 1.98 (m, 1H), 1.76 – 1.59

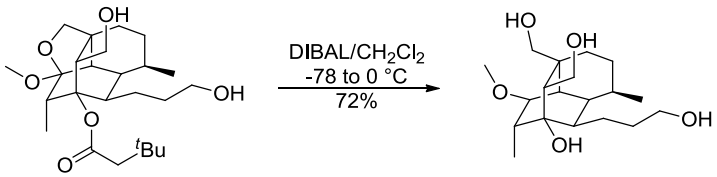
(m, 5H), 1.53 – 1.43 (m, 3H), 1.43 – 1.30 (m, 3H), 1.19 (s, 9H), 1.18 (d, J = 7.5 Hz, 3H), 0.93 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.34, 89.16, 83.42, 81.29, 62.66, 59.75, 51.53, 51.09, 49.96, 49.05, 47.61, 41.96, 38.32, 35.08, 34.82, 33.62, 32.16 (3C), 28.68, 28.00, 26.90, 21.39, 19.62, 9.50; IR (film) 3425, 2957, 2927, 2867, 1464, 1205, 1138, 1046, 985, 958, 910, 732 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{41}O_5$ $[M+H]^+$: 421.2948, found: 421.2948.



4.55 **4.56**

Alkynyl ether (13.3 mg, 0.0316 mmol) was dissolved in dichloromethane (1.5 mL) and treated with 1 N HCl (1.5 mL) for 2.0 h with vigorous stirring. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (3 × 3 mL) and brine (3 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by prep-TLC (75% ethyl acetate/hexanes) to afford a white solid (5.7 mg, 41%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.93 (t, J = 10.9 Hz, 1H), 3.74 (dd, J = 11.2, 3.3 Hz, 1H), 3.69 – 3.56 (m, 3H), 3.37 (d, J = 6.7 Hz, 1H), 3.30 (s, 2H), 3.18 (dt, J = 10.2, 2.6 Hz, 1H), 3.05 (q, J = 7.2 Hz, 1H), 2.32 – 2.24 (m, 1H), 2.21 (dt, J = 11.4, 2.0 Hz, 1H), 2.18 (s, 2H), 2.02 (m, 1H), 1.80 – 1.67 (m, 1H), 1.67 – 1.58 (m, 6H), 1.53 (m, 1H), 1.48 (d, J = 2.6 Hz, 1H), 1.43 – 1.27 (m, 3H), 1.21 – 1.17 (m, 3H), 1.04 (s, 9H), 0.90 (d, J = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.78, 108.43, 87.31, 81.56, 62.90, 60.26, 50.43, 50.11, 49.08, 47.76, 46.95, 41.95, 38.38, 36.07, 35.54,

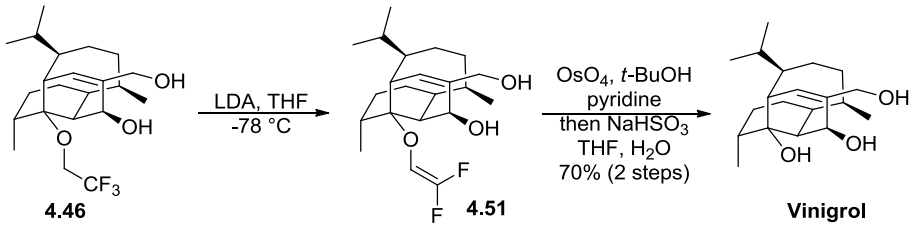
32.94, 30.91, 29.85 (3C), 28.76, 27.81, 21.38, 20.34, 9.95; IR (film) 3438, 2954, 2871, 1725, 1475, 1228, 1134, 1046, 1012, 986, 916, 732 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{25}H_{43}O_6$ $[M+H]^+$: 439.3054, found: 439.3054.



4.56 **4.57**

To a solution of ester (5.7 mg, 0.0130 mmol) in dichloromethane (0.80 mL) cooled at -78 °C, DIBAL/CH_2Cl_2 (1.0M, 0.13 mL) was added dropwise. The reaction solution was stirred at -78 °C for 30 min. then warmed to 0 °C and stirred for 2 h. The reaction was quenched with saturated Rochelle's salt solution (0.50 mL) and diluted with ethyl acetate (2.0 mL). The mixture was warmed to r.t. and stirred vigorously for 30 min. A clear two layers were formed and the upper organic layer was separated and the rest aqueous layer was extracted with ethyl acetate (3 × 2 mL). The combined organic layers were washed with brine (3.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The residue was purified by prep-TLC (10% MeOH/CH_2Cl_2) to give a colorless oil (3.2 mg, 72% yield). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.24 (dd, *J* = 10.6, 7.3 Hz, 1H), 3.88 – 3.70 (m, 3H), 3.62 (dt, *J* = 9.5, 4.4 Hz, 2H), 3.48 (d, *J* = 10.1 Hz, 1H), 3.32 (d, *J* = 10.2 Hz, 1H), 3.26 (s, 3H), 2.89 (bs, 1H), 2.38 (dt, *J* = 11.9, 2.6 Hz, 1H), 2.14 – 2.07 (m, 1H), 2.07 – 2.01 (m, 1H), 1.97 (dq, *J* = 10.3, 7.2 Hz, 1H), 1.92 – 1.83 (m, 1H), 1.83 – 1.70 (m, 2H), 1.69 – 1.53 (m, 4H), 1.45 (m, 2H), 1.32 (m, 1H), 1.15 (d, *J* = 5.8 Hz, 3H), 0.97 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, C_6D_6) δ 76.91, 76.00, 73.16, 61.48, 60.88, 57.22, 55.06, 46.94,

42.51, 38.69, 38.06, 35.83, 34.10, 33.55, 31.79, 29.60, 21.68, 19.58, 8.14; IR (film) 3340, 2921, 2875, 1458, 1375, 1193, 1062, 1015, 909, 731 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{19}H_{35}O_5$ $[M+H]^+$: 343.2479, found: 343.2478.

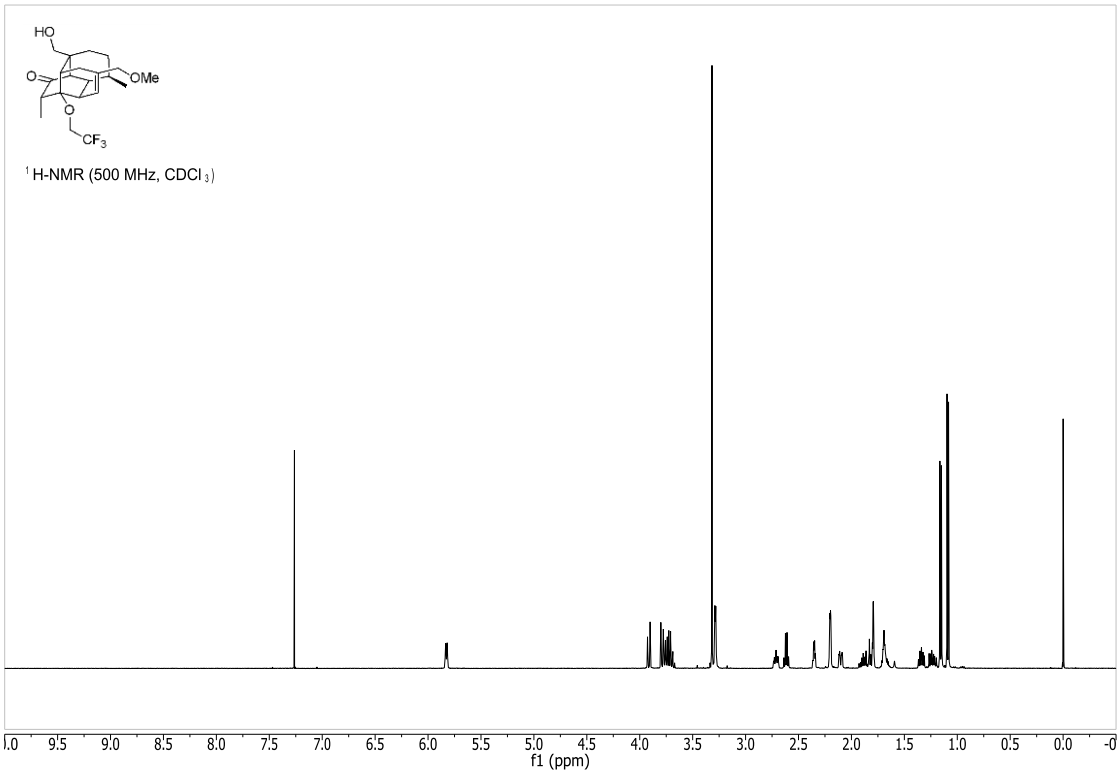


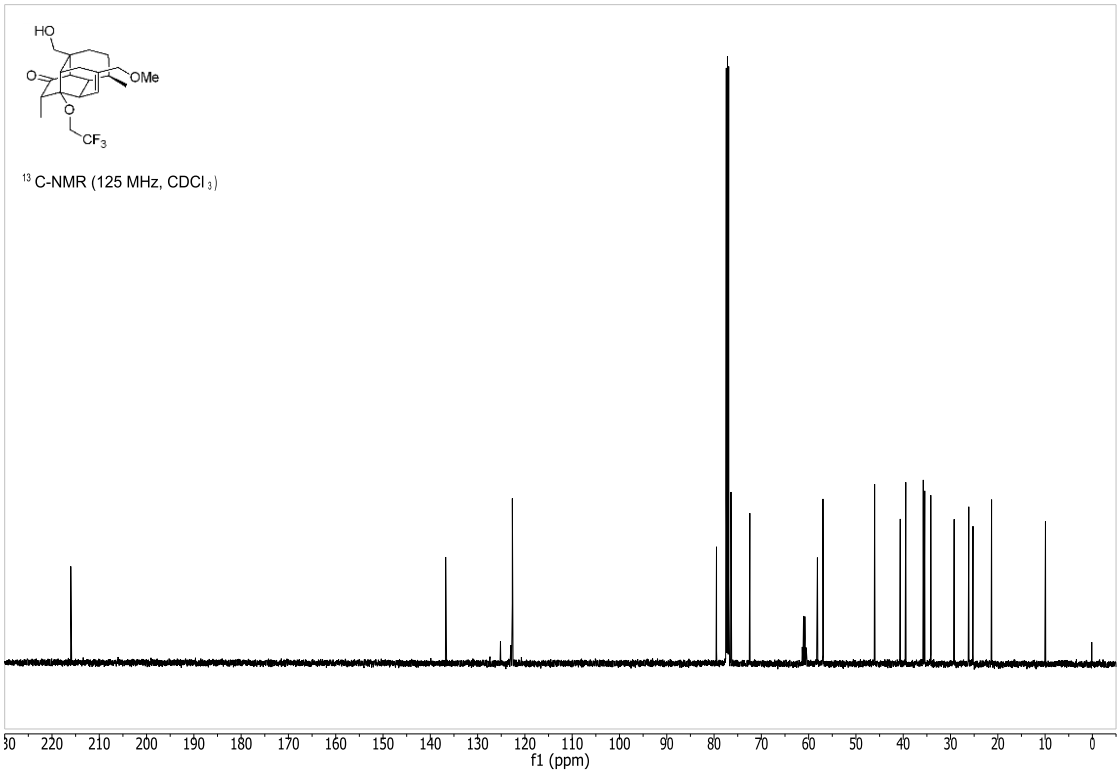
To a solution of trifluoroethyl ether (0.7 mg, 0.0017 mmol) in THF (0.15 mL), freshly prepared LDA (0.5 M in THF, 0.27 mL, 0.136 mmol) was added slowly at -78 °C. After the addition was completed, the reaction was stirred at -78 °C for 30 min. then quenched by saturated NH_4Cl solution (0.5 mL) and extracted with ethyl acetate (3 × 1.0 mL). The combined extracts were washed with brine (1.5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. ^{1}H-NMR analysis of crude product indicated 25% conversion of starting material to product. The crude product was purified by prep-TLC (60% diethyl ether/hexanes) to provide the unreacted starting material and the product. The isolated starting material was re-subjected to the same reaction conditions. After three iterations, approximate 0.6 mg of desired product was obtained (judging by the integration of the ^{1}H-NMR peaks of solvent and product).

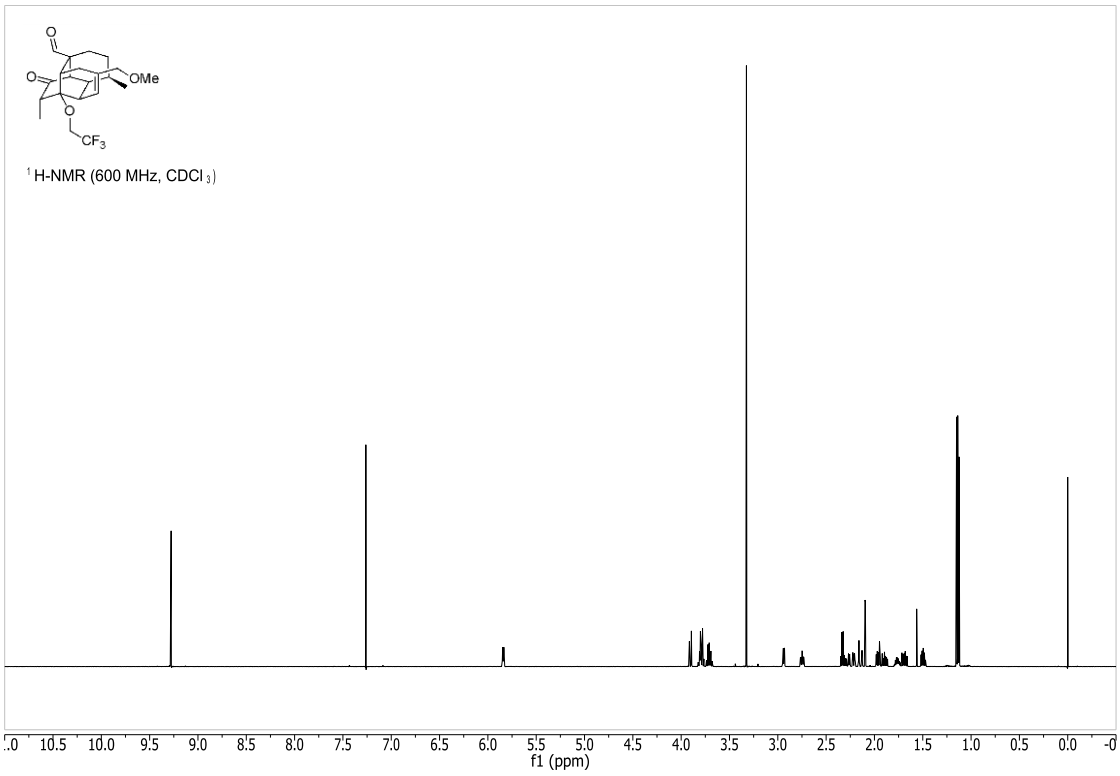
The resultant difluorovinyl ether was dissolved in pyridine (0.30 mL) and osmium tetroxide (2.5 wt% in *tert*-butanol, 0.05 mL, 0.0039 mmol) was added at r.t. After stirring for 30 min., the reaction was quenched by saturated $NaHSO_3$ solution (1.5 mL), diluted with THF (1.0 mL) and stirred vigorously at r.t. for 8.0 h. The

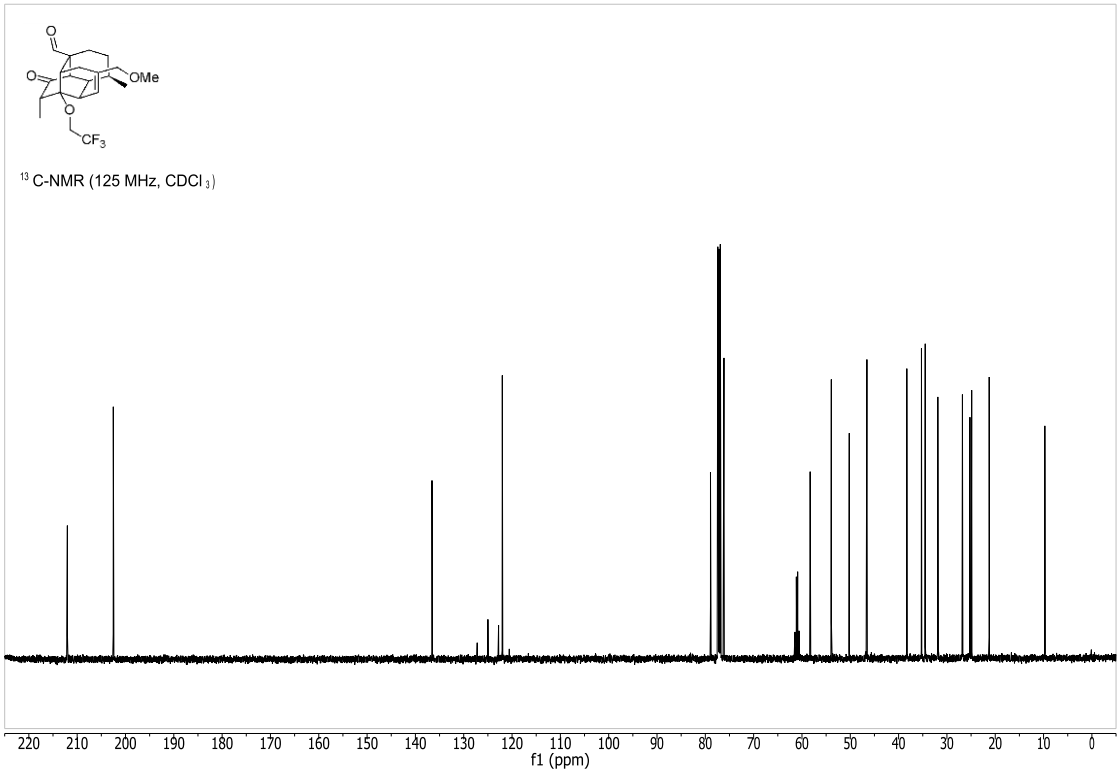
reaction mixture was extracted with ethyl acetate (3 × 2.0 mL), washed with brine (2.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. The crude product was purified by a short column (50% acetonitrile/benzene) to give approximate 0.4 mg of product (judging by the integration of the ^{1}H-NMR peaks of solvent and product, 70% yield for two steps). ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.84 (d, *J* = 5.6 Hz, 1H), 4.30 (AB q, *J* = 12.0 Hz, 2H), 4.19 (s, 1H), 3.30 (bs, 1H), 2.45 (bs, 1H), 2.30 (d, *J* = 5.6 Hz, 1H), 2.26 (d, *J* = 3.9 Hz, 1H), 2.15 – 2.09 (m, 1H), 2.03 – 1.93 (m, 2H), 1.81 – 1.71 (m, 2H), 1.66 – 1.53 (m, 3H), 1.40 – 1.10 (m, 6H), 1.00 – 0.95 (m, 9H), 0.90 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (extracted from HSQC and HMBC spectra) δ 136.8, 128.4, 75.6, 72.8, 67.9, 51.3, 45.8, 44.2, 40.4, 35.9, 34.7, 33.1, 29.6, 29.0, 28.7, 27.3, 24.9, 21.5, 20.6, 15.4; IR (film) 3405, 2954, 2925, 2869, 2855, 1559, 1462, 1386, 1106, 1017, 998, 904, 736, 701 cm^{-1}; HRMS (ESI) *m/z* calcd. for $C_{20}H_{34}O_3Li$ $[M+Li]^+$: 329.2662, found: 329.2662.

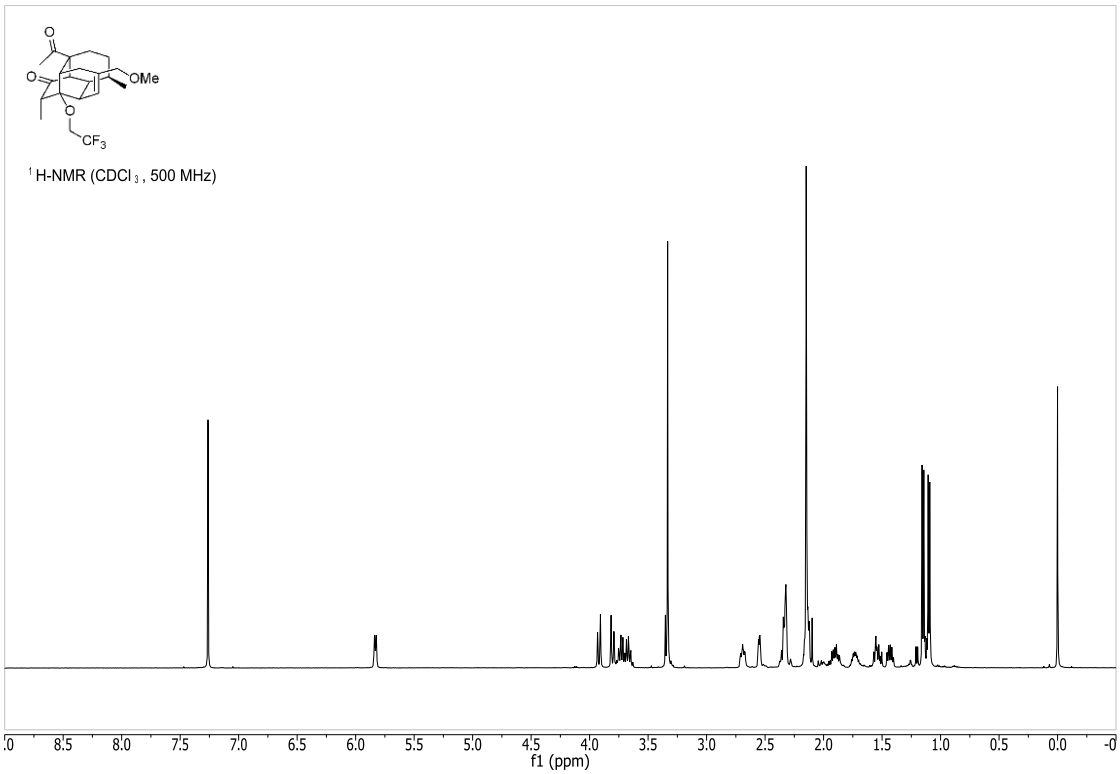
A3.2 ^{1}H and ^{13}C-NMR spectra for Chapter 4

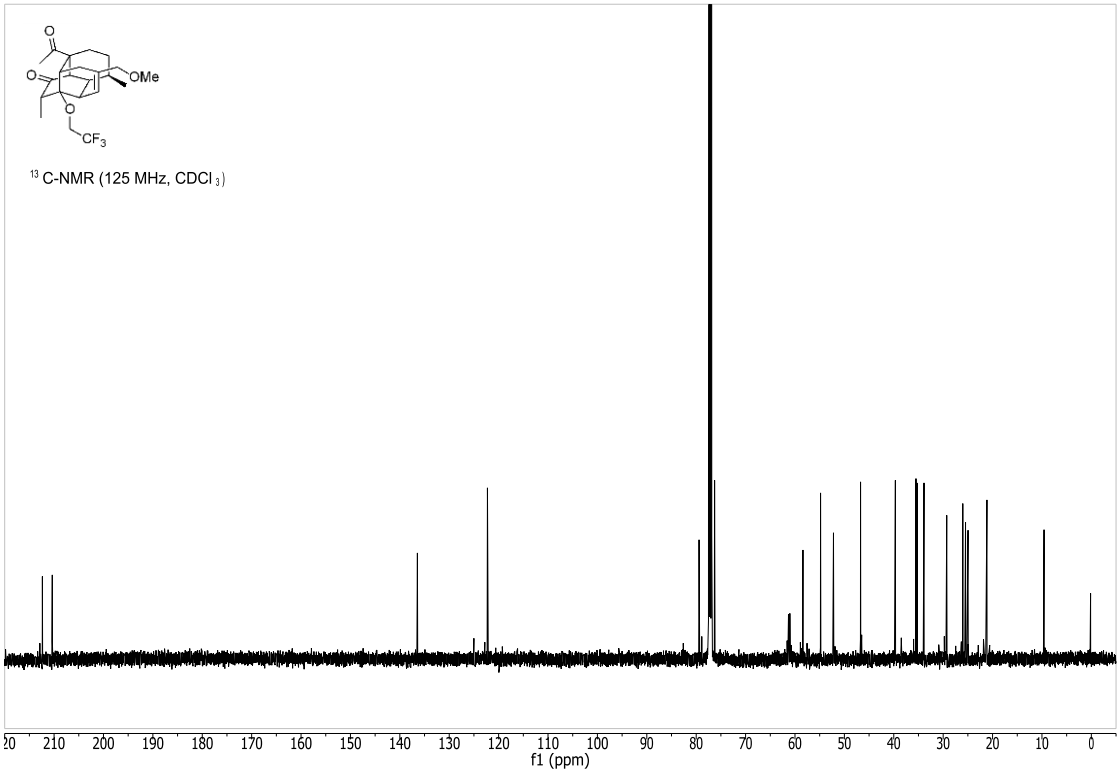


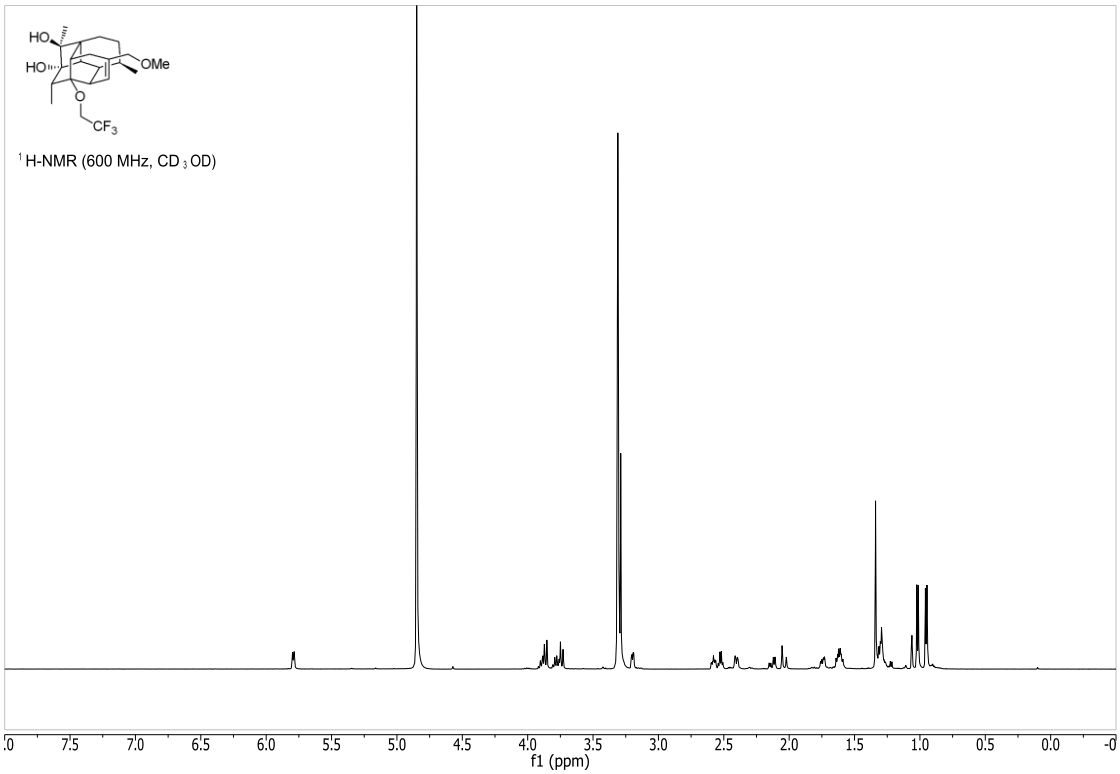


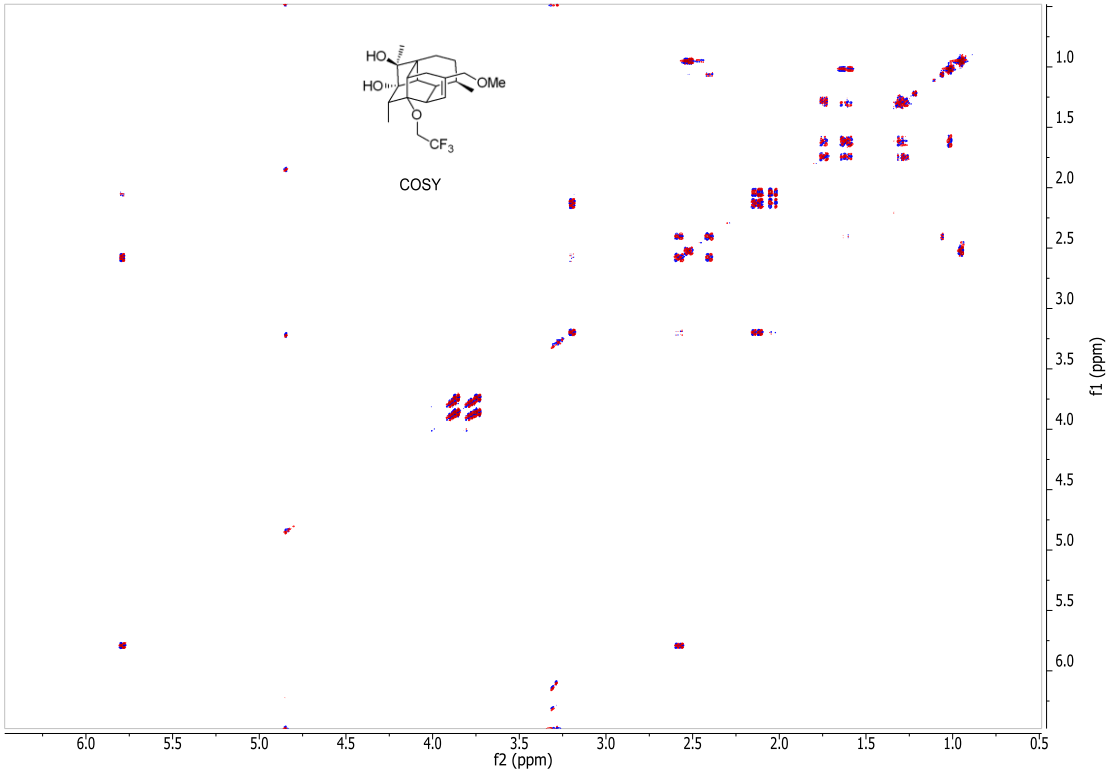

O
O
OMe
O
CF3
1 H-NMR (600 MHz, CDCl 3)
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


O
O
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OMe
CF3
1 H-NMR (CDCl 3 , 500 MHz)
f1 (ppm)


OMe
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


HO
HO
OMe
O
CF3
1H-NMR (600 MHz, CD3OD)
f1 (ppm)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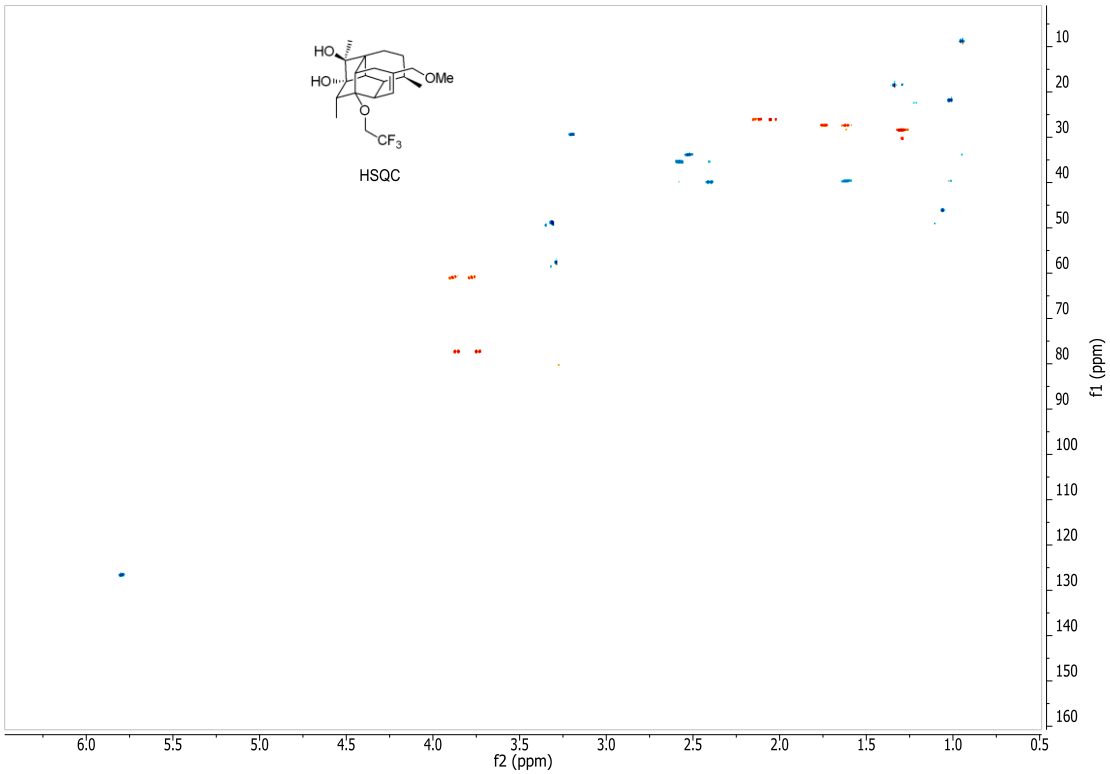
HO
OMe
O
CF3
COSY
f2 (ppm)
f1 (ppm)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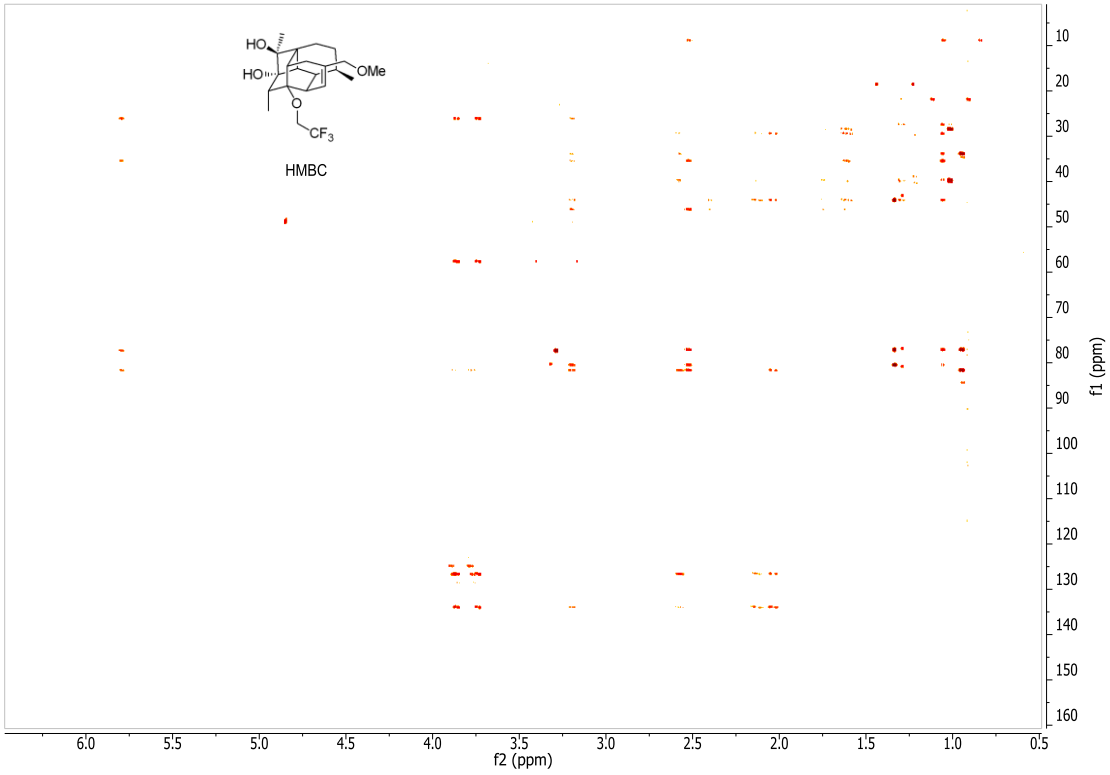
HO
OMe
O
CF3
HSQC
f1 (ppm)
f2 (ppm)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HO
OMe
O
CF3
HMBC
f1 (ppm)
f2 (ppm)

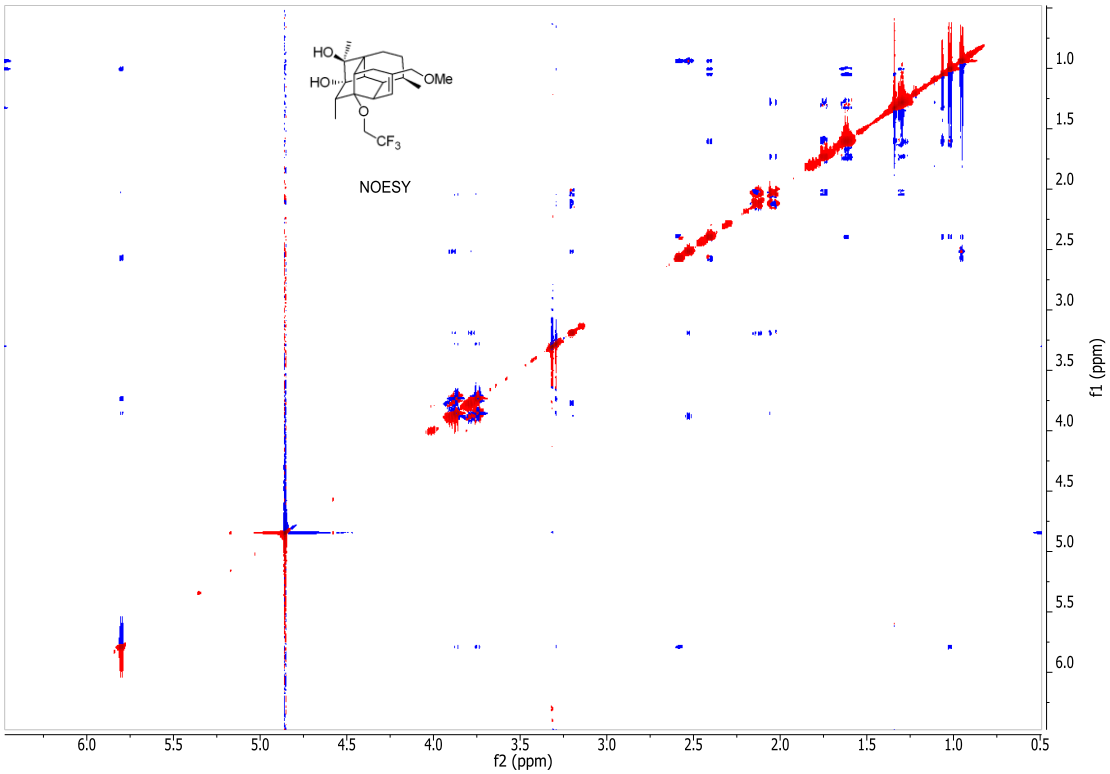
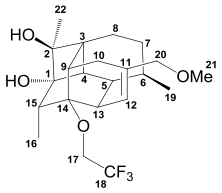
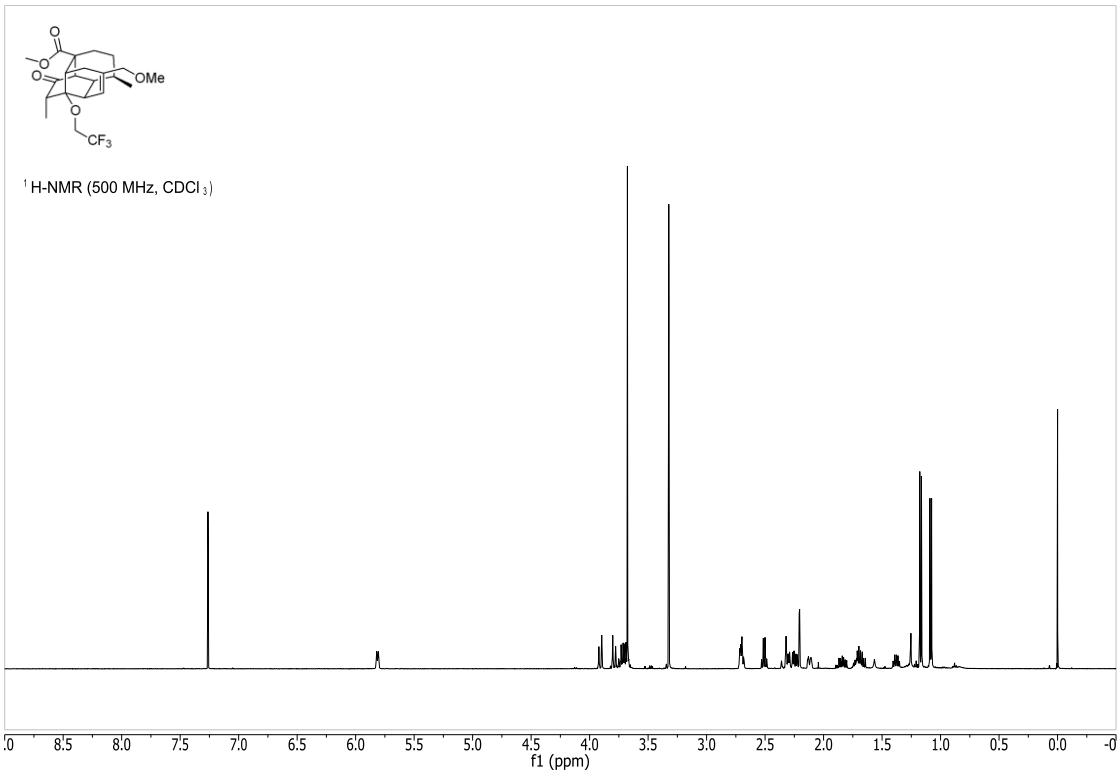
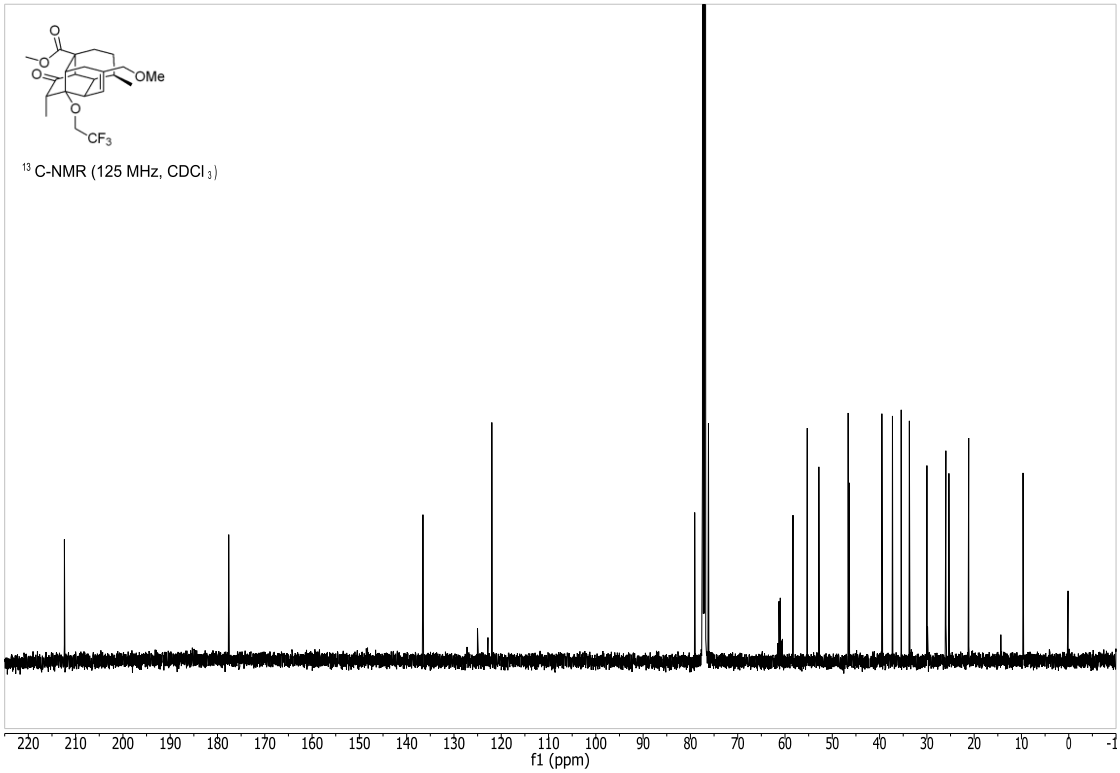

HO
HO
OMe
O
CF3
NOESY
f2 (ppm)
f1 (ppm)

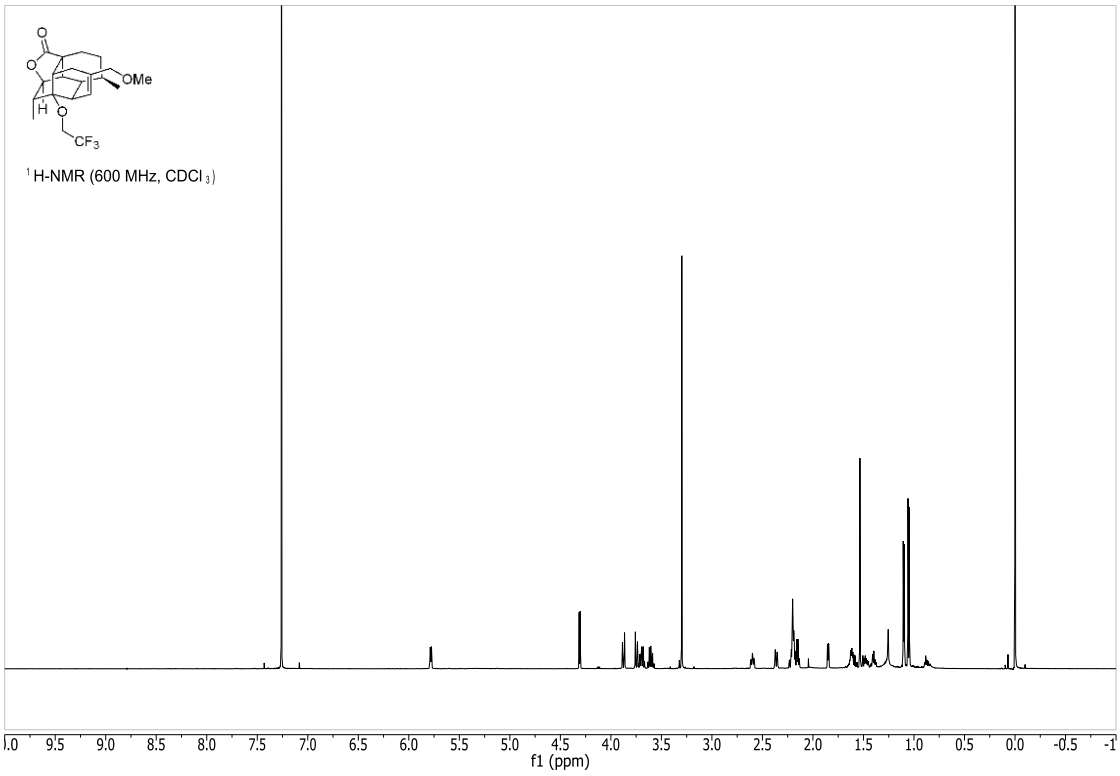
Table A3.1. 2D-NMR Data of Compound **4.10**

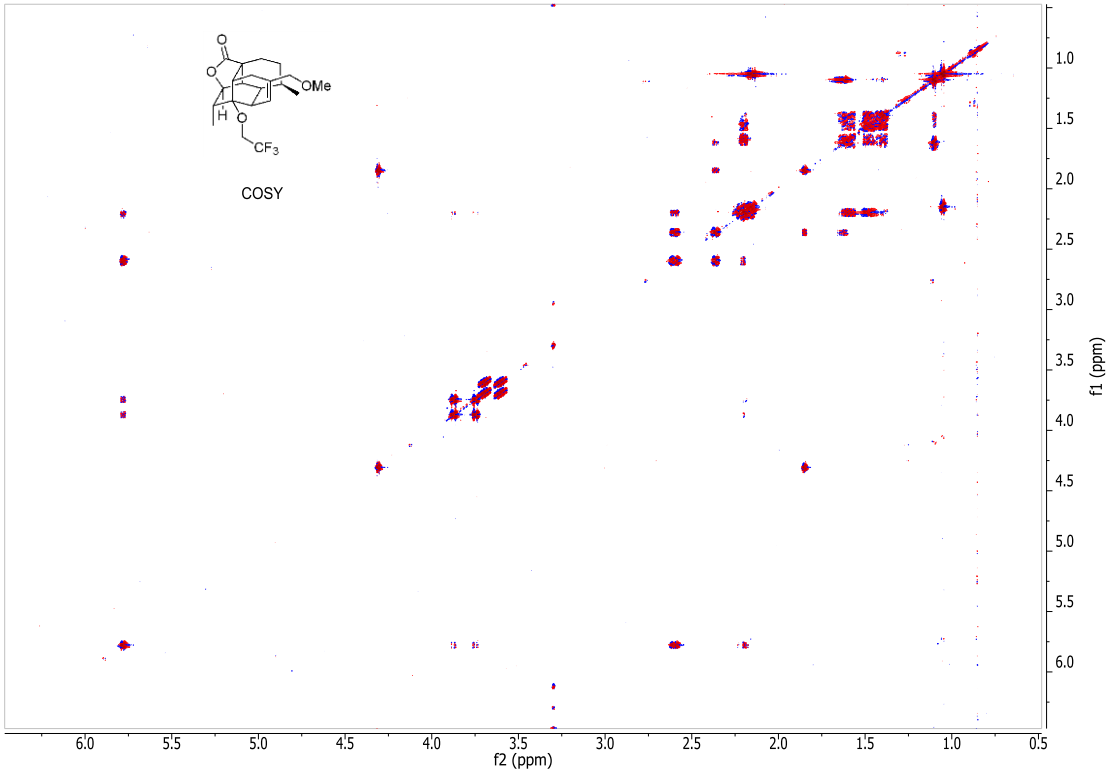


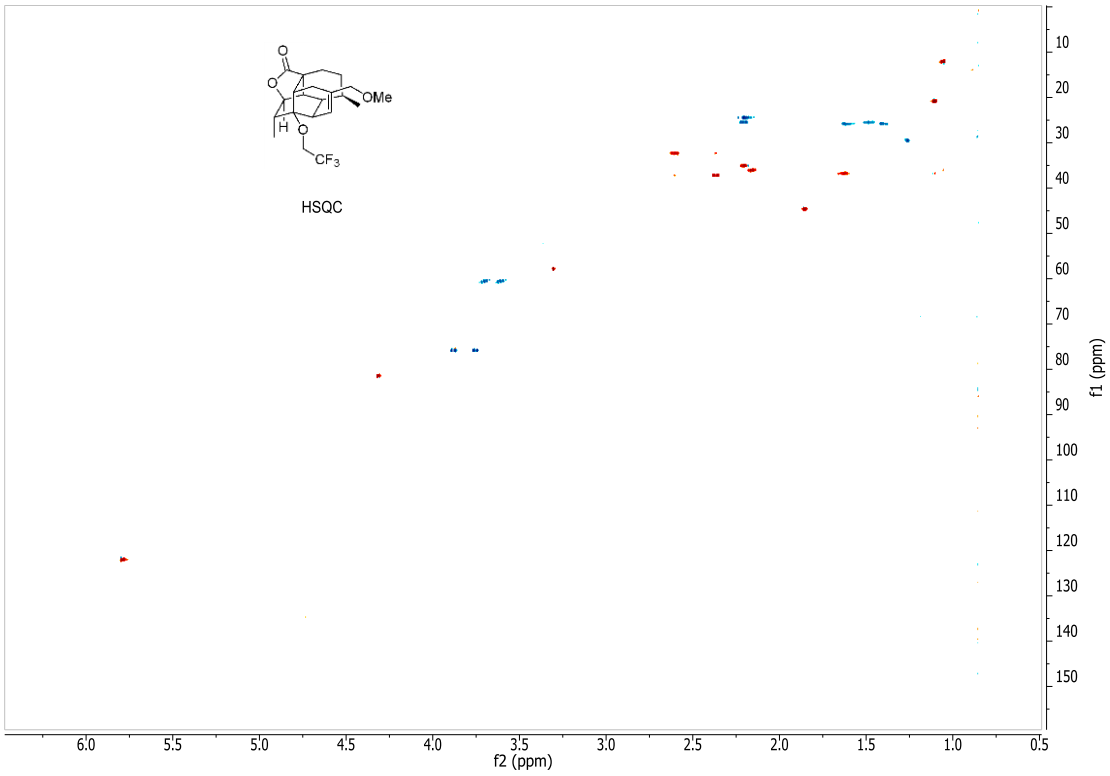
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	NOESY correlations
1	77.30		Cq			
2	80.67		Cq			
3	44.21		Cq			
4	46.27	1.06	CH	H-5	C-2, C-1, C-3, C-6, C-13, C-15, C-9, C-7, C-16	H-22
5	40.00	2.40	CH	H-13, H-4	C-3	H-6, H-19, H-16
6	39.88	1.61	CH	H-19, H-5	C-13	H-5, H-8a
7a	27.57	1.62	CH_2	H-8a, H-8b, H-7b	C-4, C-3, C-8, C-9	
7b		1.75		H-7a, H-8a, H-8b	C-4,C-3, C-8, C-9	H-10a
8a	28.55	1.30	CH_2	H-7b, H-7a		
8b		1.30			C-1, C-2, C-3	
9	29.58	3.20	CH	H-13, H-10a, H-10b	C-11, C-14, C-2, C-3, C-4, C-13, C-15, C-10	H-17a, H-15, H-10b, H-10a
10a	26.28	2.04	CH_2	H-12, H-9, H-10b	C-11, C-12, C-3, C-9	H-8a, H-7b
10b		2.13		H-12, H-9, H-10b	C-11, C-12, C-3, C-9	
11	133.99		Cq			
12	126.65	5.79	CH	H-20a, H-20b, H-13, H-10a, H-10b	C-14, C-20, C-13, C-10	H-20a, H-20b, H-13, H-19
13	35.60	2.57	CH	H-12, H-9, H-5	C-11, C-12, C-14, C-5, C-15, C-9	H-12, H-5, H-16
14	81.85		Cq			
15	34.08	2.52	CH	H-16	C-14, C-2, C-1, C-4, C-13, C-16	H-17b, H-16
16	9.02	0.95	CH_3	H-15	C-14, C-1, C-15	
17a	61.12	3.77	CH_2	H-17b	C-14, C-18	H-9, H-15
17b		3.89		H-17a	C-14, C-18	H-9, H-15
18	125.79		Cq			
19	22.04	1.02	CH_3	H-6	C-6, C-18	H-5
20a	77.43	3.74	CH_2	H-10a, H-12, H-20b	C-11, C-12, C-21, C-10	H-12, H-21, H-10a
20b		3.86		H-10a, H-12, H-20a	C-11, C-12, C-21, C-10	H-12, H-21, H-10a
21	57.70	3.29	CH_3		C-20	
22	18.73	1.34	CH_3		C-2, C-1, C-3	

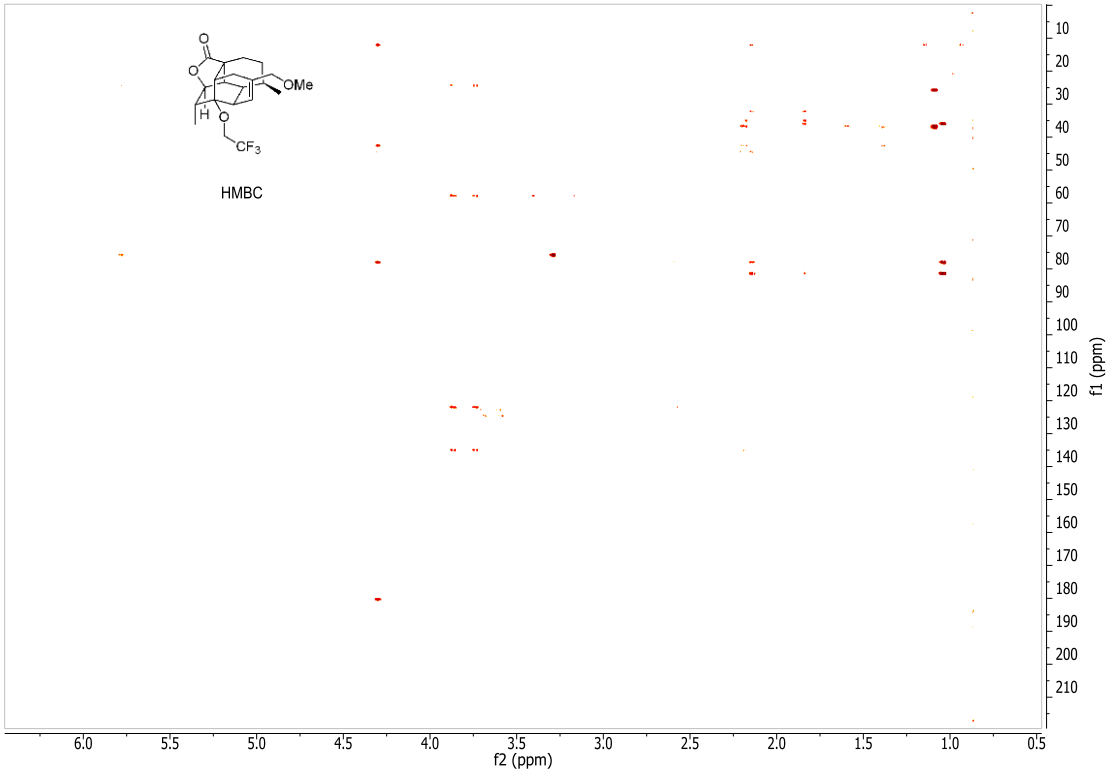

OMe
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)


OMe
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


OMe
H
O
CF3
1H-NMR (600 MHz, CDCl3)
f1 (ppm)


OMe
H
O
CF3
COSY
f2 (ppm)
f1 (ppm)


HSQC
OMe
H
O
CF3
f2 (ppm)
f1 (ppm)


HMBC
OMe
H
O
CF3
f2 (ppm)
f1 (ppm)

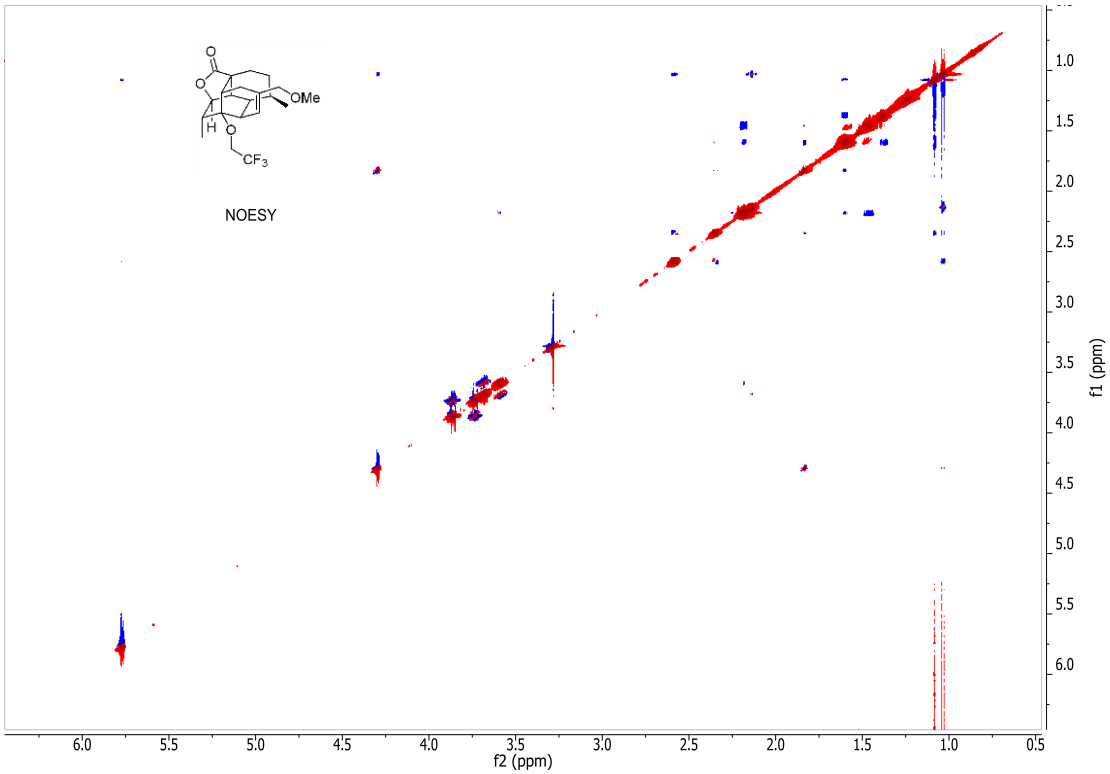
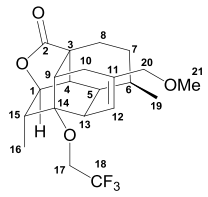
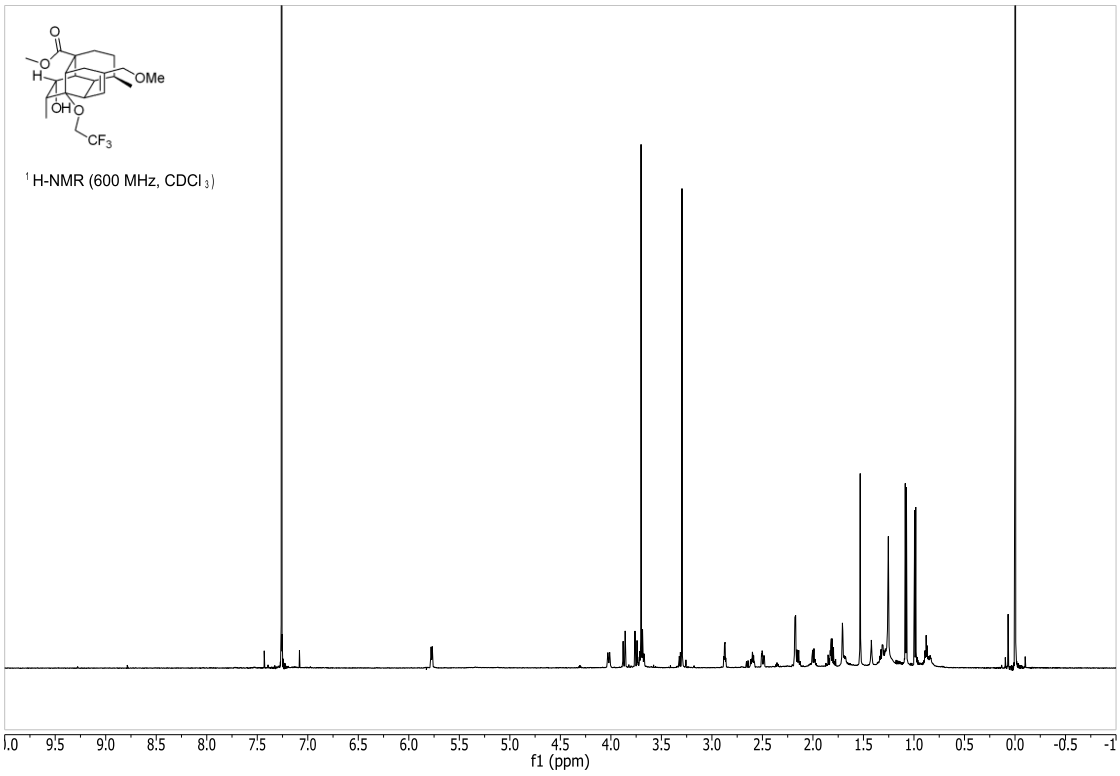
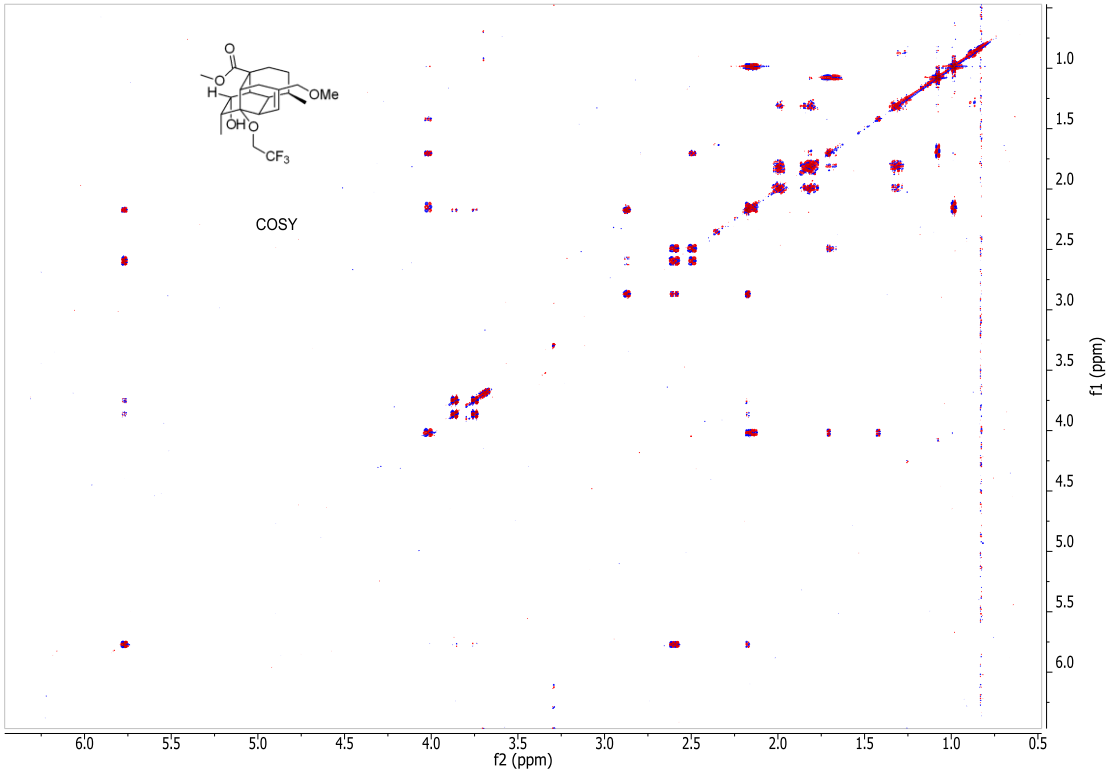

OMe
H
O
CF3
NOESY
f2 (ppm)
f1 (ppm)

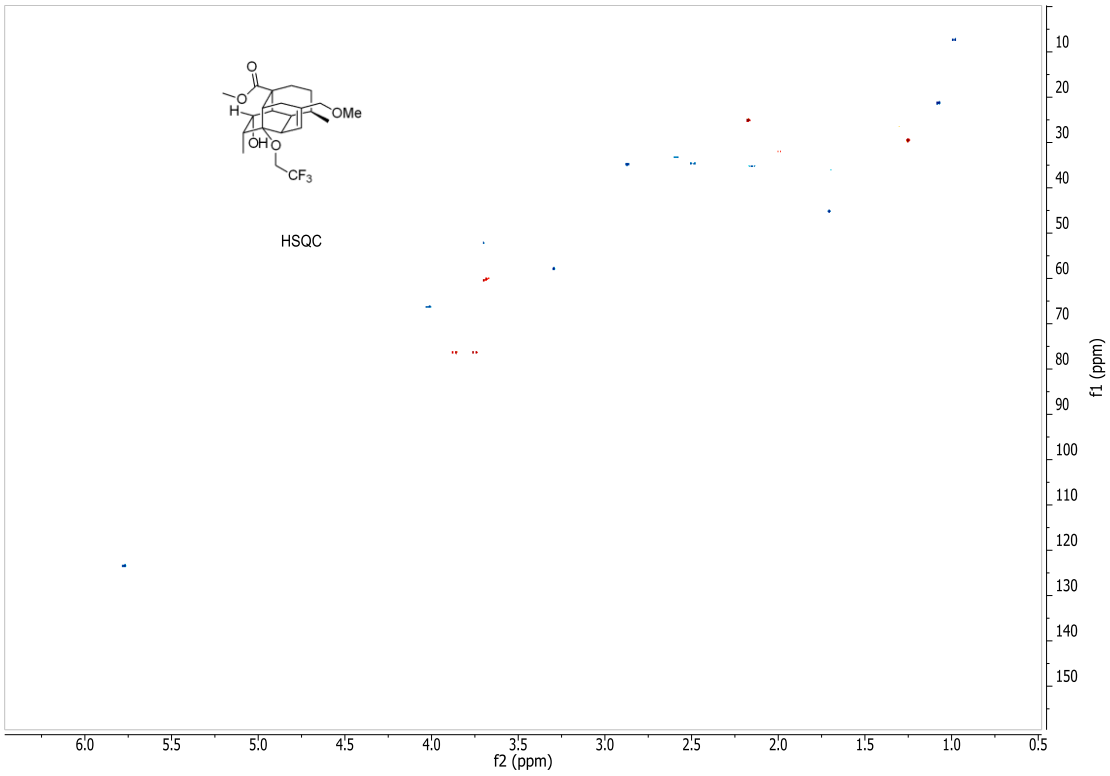
Table A3.2. 2D-NMR Data of Compound **4.14**

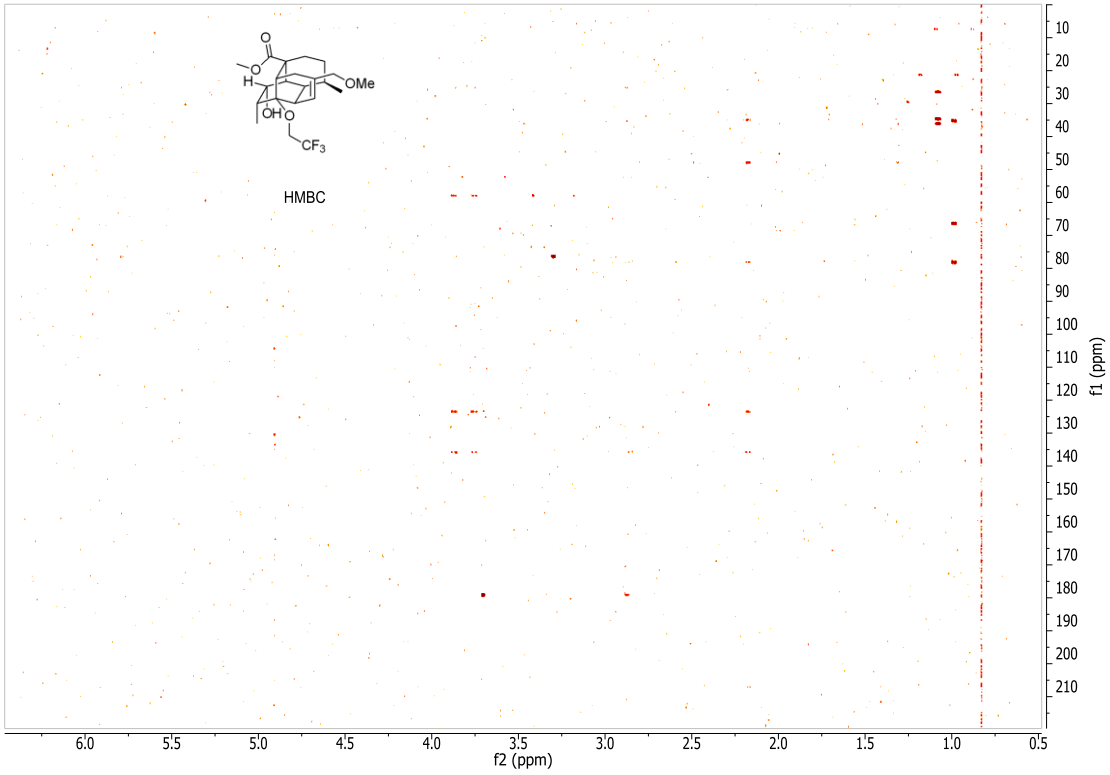


Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	NOESY correlations
1	81.67	4.31	CH	H-4	C-2, C-14, C-4, C-3, C-16	H-16
2	189.27		Cq			
3	42.90		Cq			
4	44.90	1.85	CH	H-1, H-5	C-1, C-15, C-9, C-13	H-5, H-6, H-8b, H-7a
5	37.42	2.36	CH	H-13, H-4, H-6		H-4, H-6, H-19, H-16
6	37.07	1.63	CH	H-5, H-19		H-5
7a	25.72	1.48	CH_2	H-7b, H-8b		
7b		2.20		H-8b, H-7a, H-8a		
8a	26.01	1.40	CH_2	H-7b, H-8b	C-3, C-6	
8b		1.61		H-7b, H-8a	C-6	
9	35.32	2.20	CH	H-13		H-17a
10a	24.73	2.20	CH_2	H-12, H-20a, H-20b		
10b		2.20		H-12, H-20a, H-20b		
11	135.14		Cq			
12	122.12	5.78	CH	H-20a, H-20b, H-13, H-10a, H-10b	C-14, C-20, C-13, C-10	H-20a, H-20b, H-13
13	32.54	2.60	CH	H-12, H-5, H-9	C-12, C-14	H-12, H-19
14	78.27		Cq			
15	36.34	2.15	CH	H-16	C-1, C-14, C-4, C-9, C-13, C-16	H-17b, H-16
16	12.41	1.05	CH_3	H-15	C-1, C-14, C-15	H-13, H-15
17a	60.79	3.59	CH_2	H-17b	C-18	H-9
17b		3.69		H-17a	C-18	H-15
18	123.80		Cq			
19	21.13	1.10	CH_3	H-6	C-6, C-7	H-5
20a	75.98	3.75	CH_2	H-12, H-10a, H-10b, H-20b	C-11, C-12, C-21, C-10	H-12, H-21, H-10a, H-10b
20b		3.88		H-12, H-10a, H-10b, H-20a	C-11, C-12, C-21, C-10	H-12, H-21, H-10a, H-10b
21	58.10	3.30	CH_3		C-20	


OMe
OH
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)


OMe
OH
O
CF3
COSY
f2 (ppm)
f1 (ppm)


HSQC
OMe
OH
O
CF3
f2 (ppm)
f1 (ppm)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CF3
f2 (ppm)
f1 (ppm)

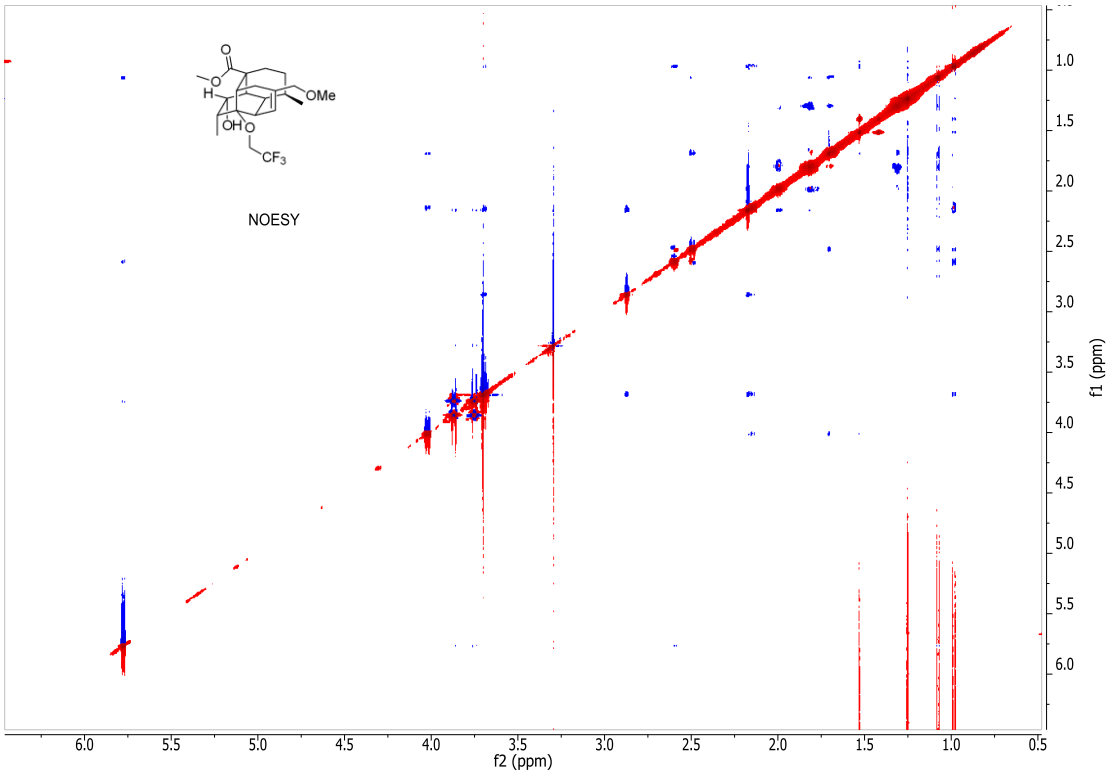
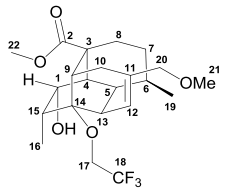
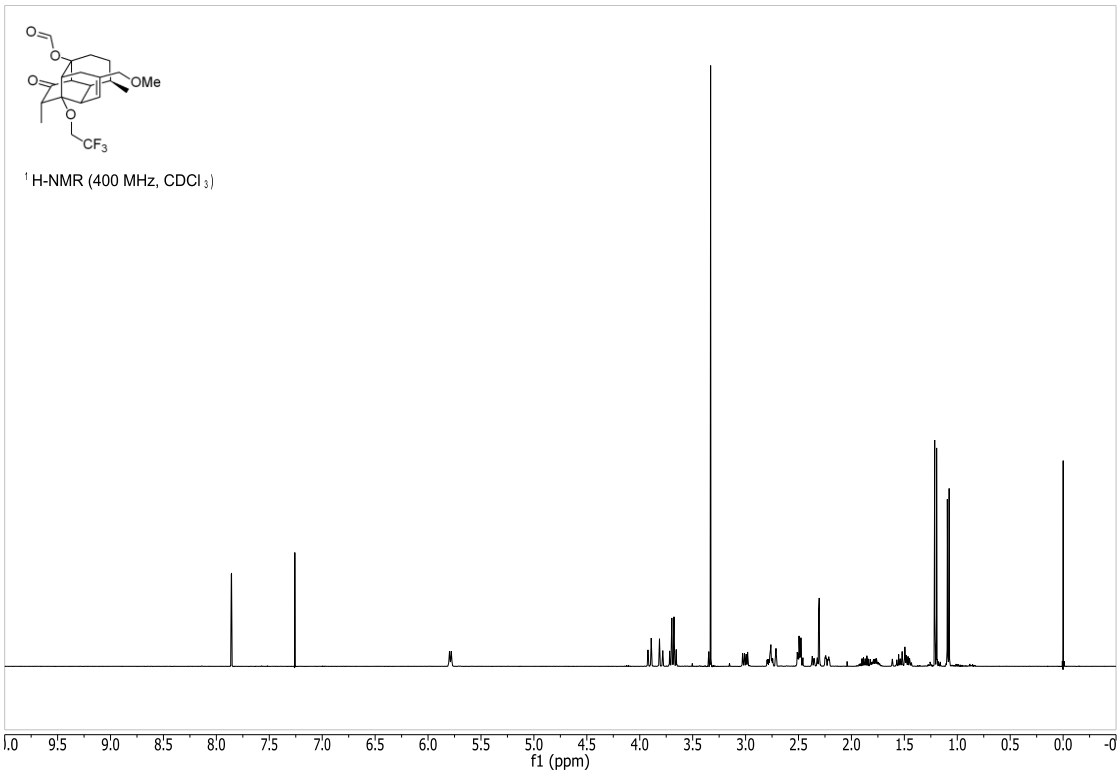
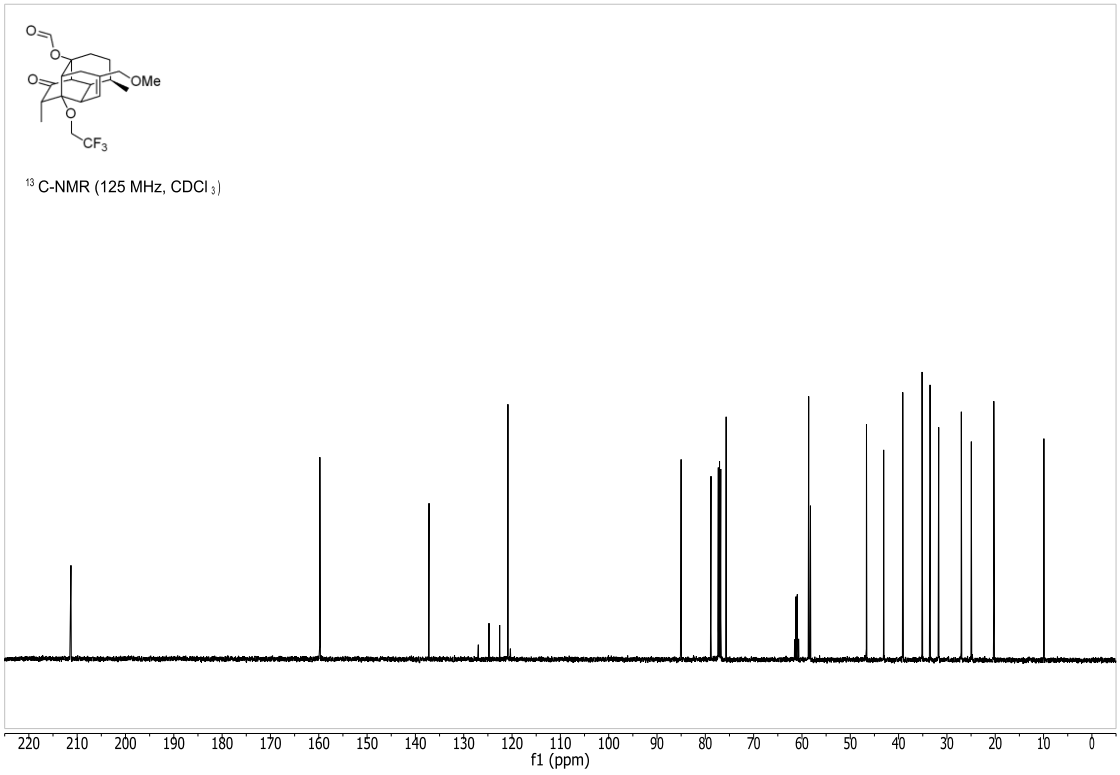

NOESY
OMe
OH
CF3
f2 (ppm)
f1 (ppm)

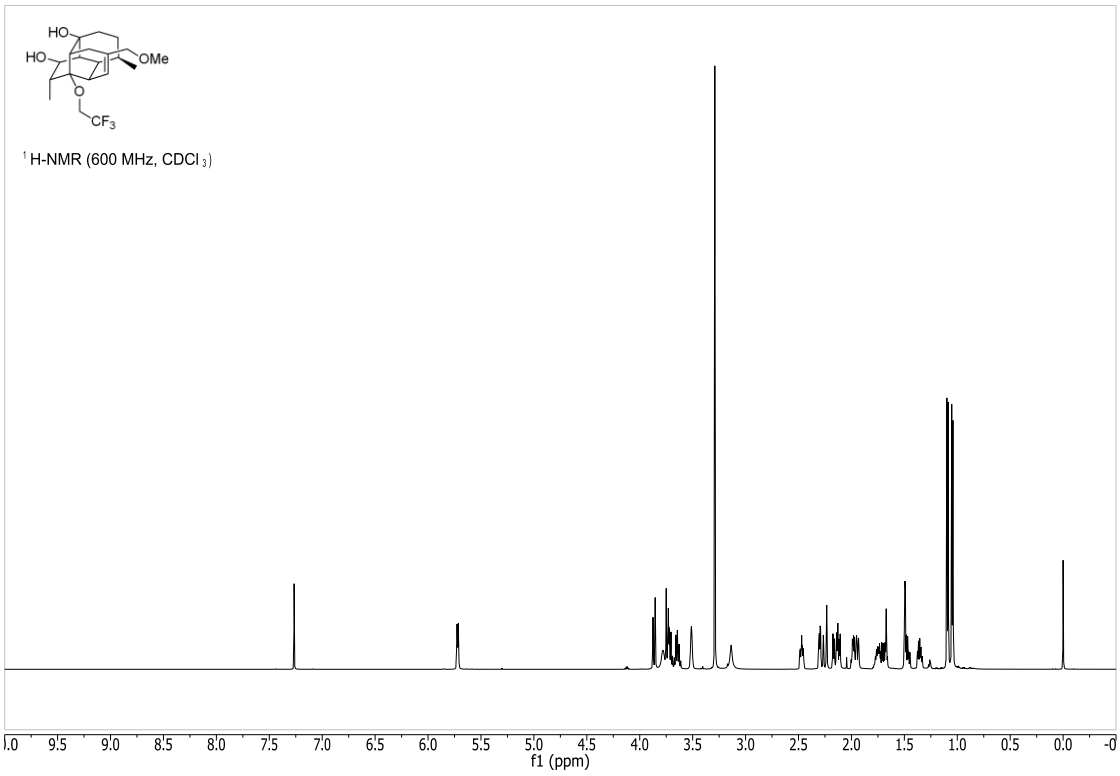
Table A3.3. 2D-NMR Data of Compound **4.15**

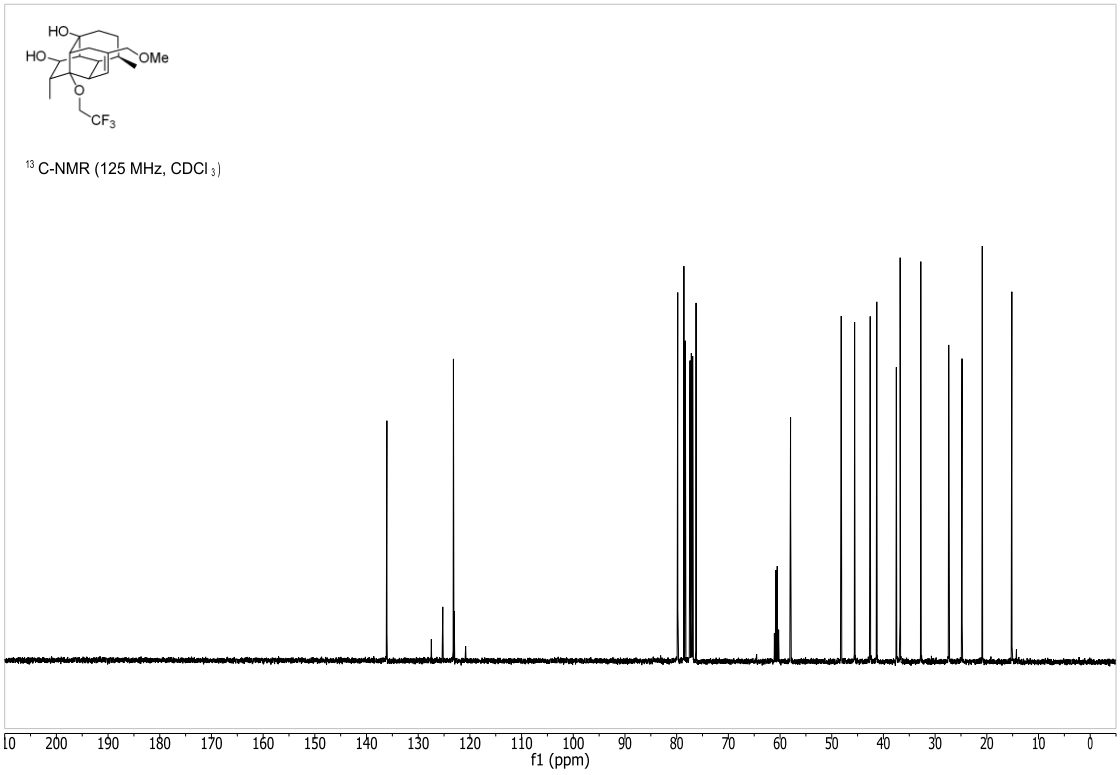


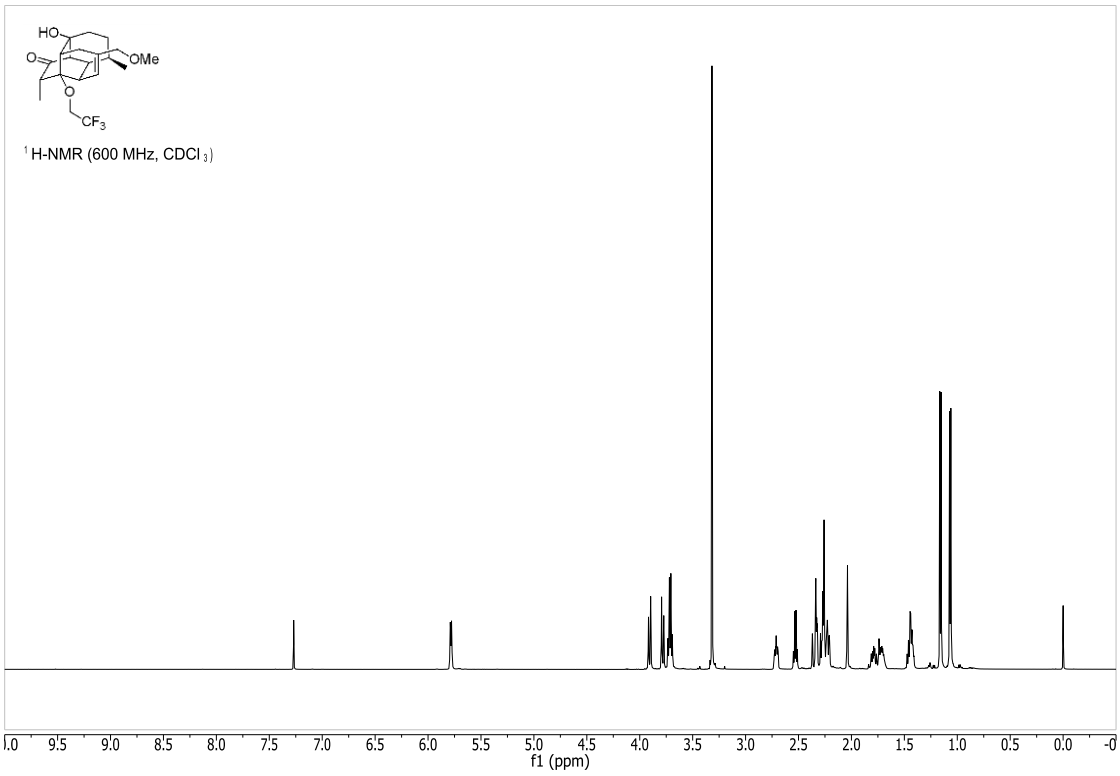
Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations	NOESY correlations
1	66.39	4.02	CH	H-15, H-4, H-23		H-15, H-4
2	179.14		Cq			
3	48.06		Cq			
4	45.36	1.71	CH	H-1, H-5	C-14, C-5	H-5
5	34.85	2.50	CH	H-13, H-6		H-4, H-19, H-16
6	36.19	1.69	CH	H-7b, H-19		H-7a, H-19
7a	26.75	1.31	CH_2	H-8b, H-7b		H-8b, H-6
7b		1.83		H-8b, H-7a		
8a	32.25	1.81	CH_2	H-8b, H-7a		
8b		2.00		H-8a, H-7a		H-10, H-8a, H-7a
9	35.05	2.87	CH	H-13, H-10	C-2, C-11, C-10	H-22, H-15
10a	25.33	2.17	CH_2	H-12, H-9	C-11, C-12, C-3, C-9	H-9
10b		2.17				
11	135.80		Cq			
12	123.51	5.77	CH	H-20a, H-20b, H-13, H-10	C-20	H-20a, H-20b, H-13, H-19
13	33.45	2.60	CH	H-12, H-9, H-5		H-12, H-16
14	78.32		Cq			
15	35.38	2.15	CH	H-1, H-16	C-14	H-1, H-22, H-9, H-16
16	7.59	0.99	CH_3	H-15	C-14, C-1, C-15	H-13, H-17, H-5, H-15
17a	60.58	3.69	CH_2			H-16
17b		3.69				H-16
18	124.30		Cq			
19	21.48	1.08	CH_3	H-6	C-6, C-5, C-7	
20a	76.61	3.75	CH_2	H-20b, H-10	C-11, C-12, C-21	H-10, H-12
20b		3.87		H-20a, H-10	C-11, C-12, C-21	H-10, H-12
21	58.03	3.30	CH_3		C-20	
22	52.38	3.70	CH_3		C-2	H-9
23		1.42	OH	H-1		

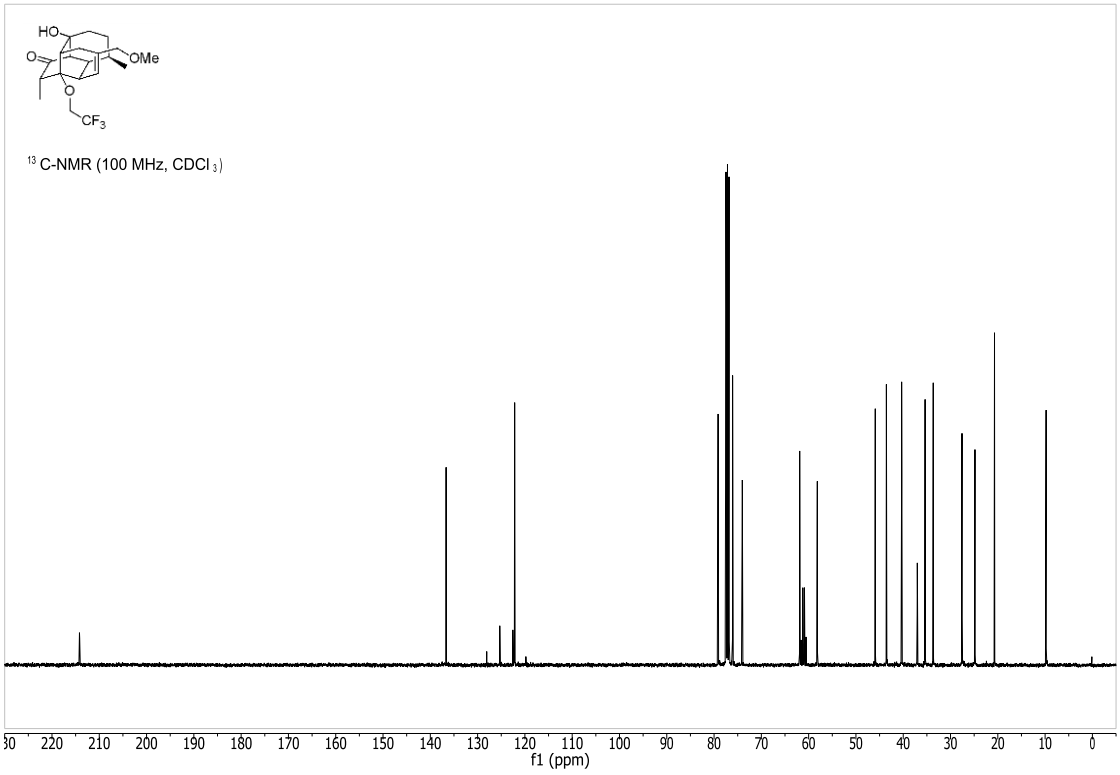

OMe
CF3
1 H-NMR (400 MHz, CDCl 3)
f1 (ppm)

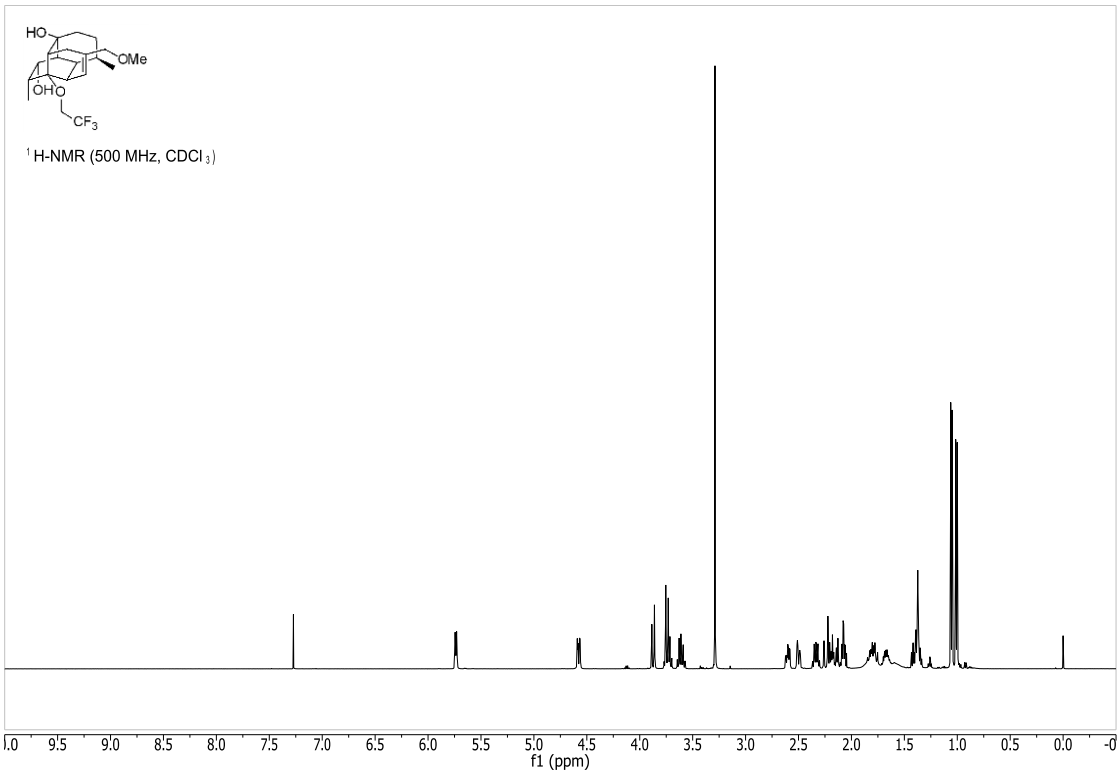

OMe
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

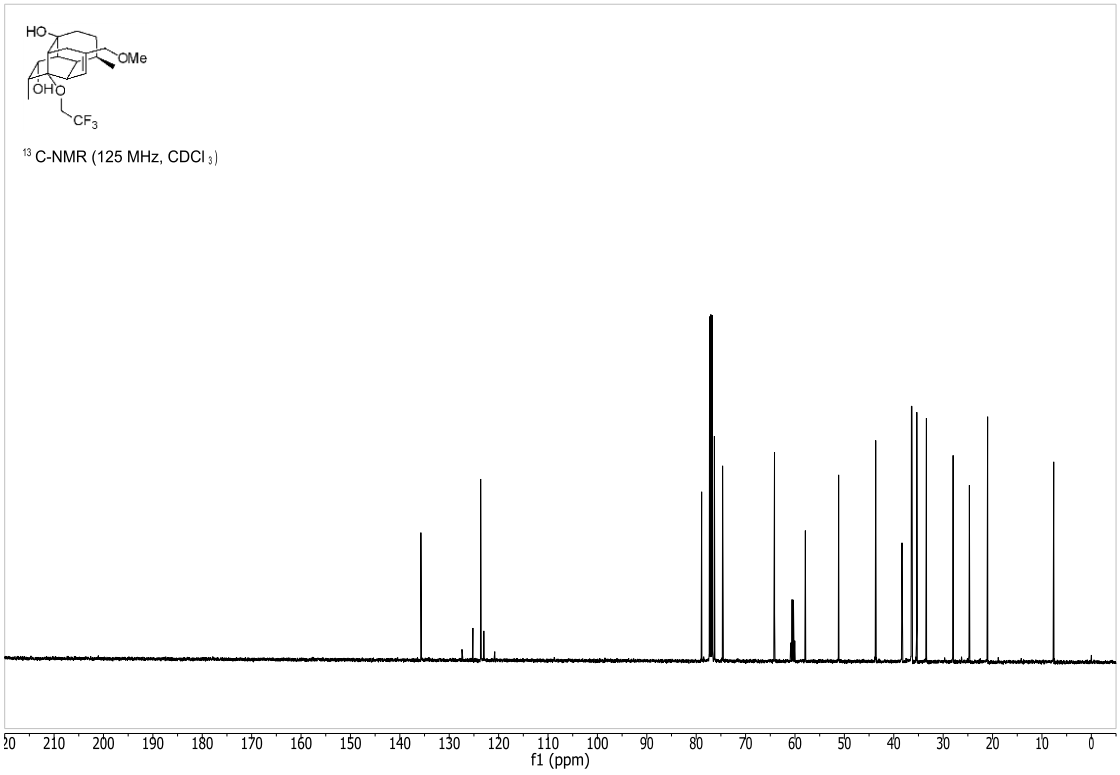

HO
HO
OMe
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

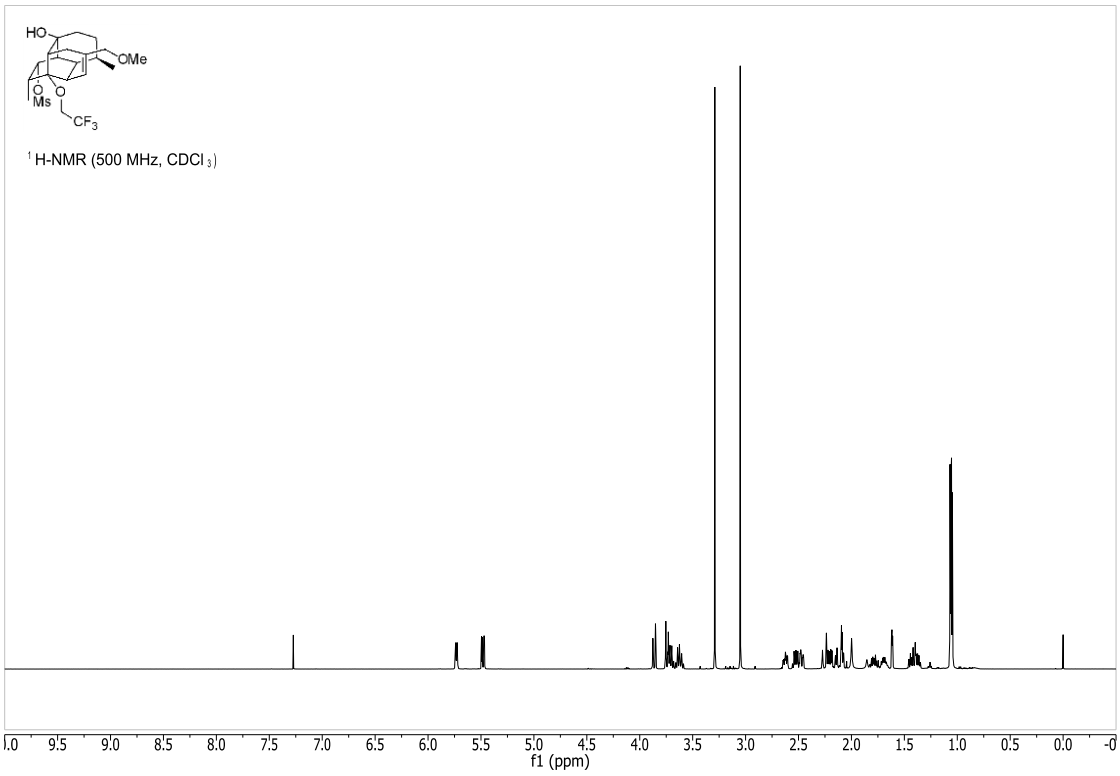

HO
HO
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

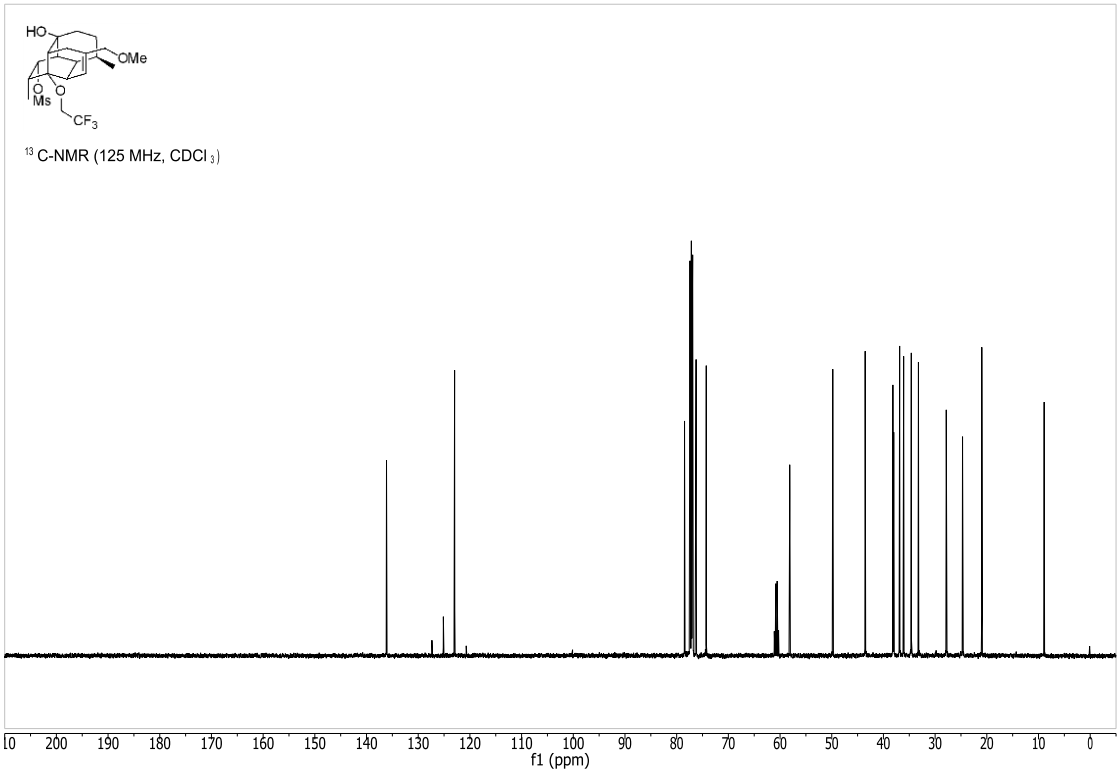

HO
O
OMe
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

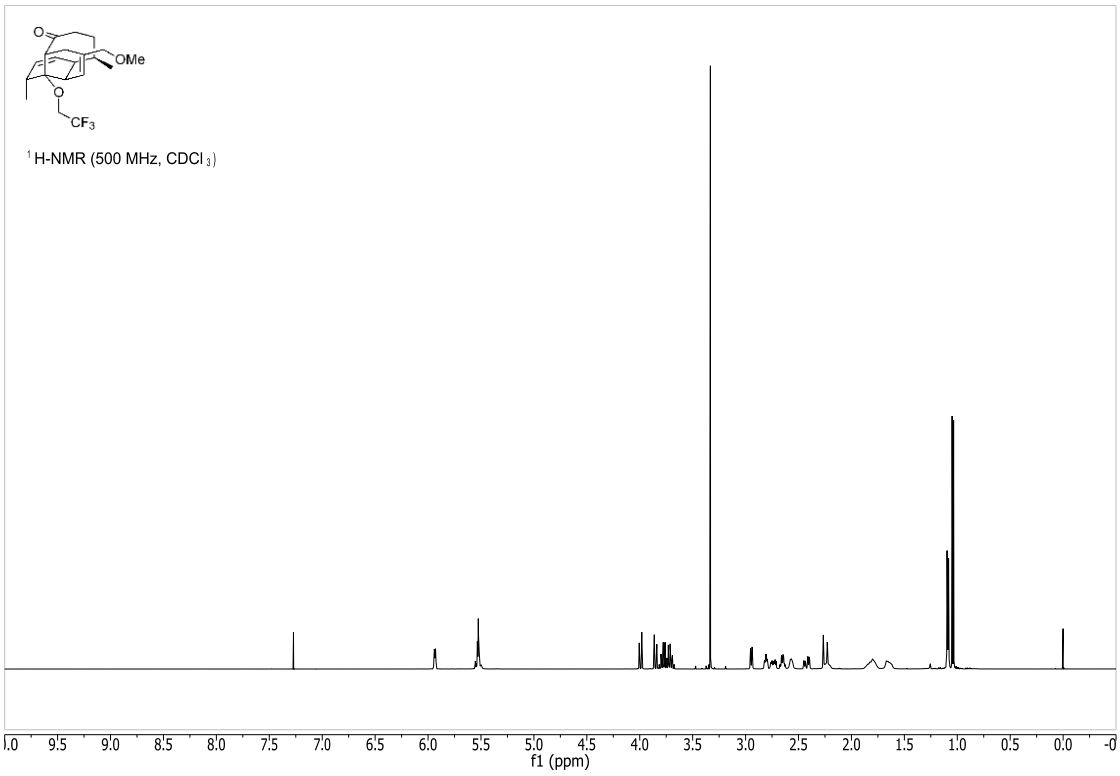

HO
O
OMe
O
CF3
13 C-NMR (100 MHz, CDCl 3)
f1 (ppm)

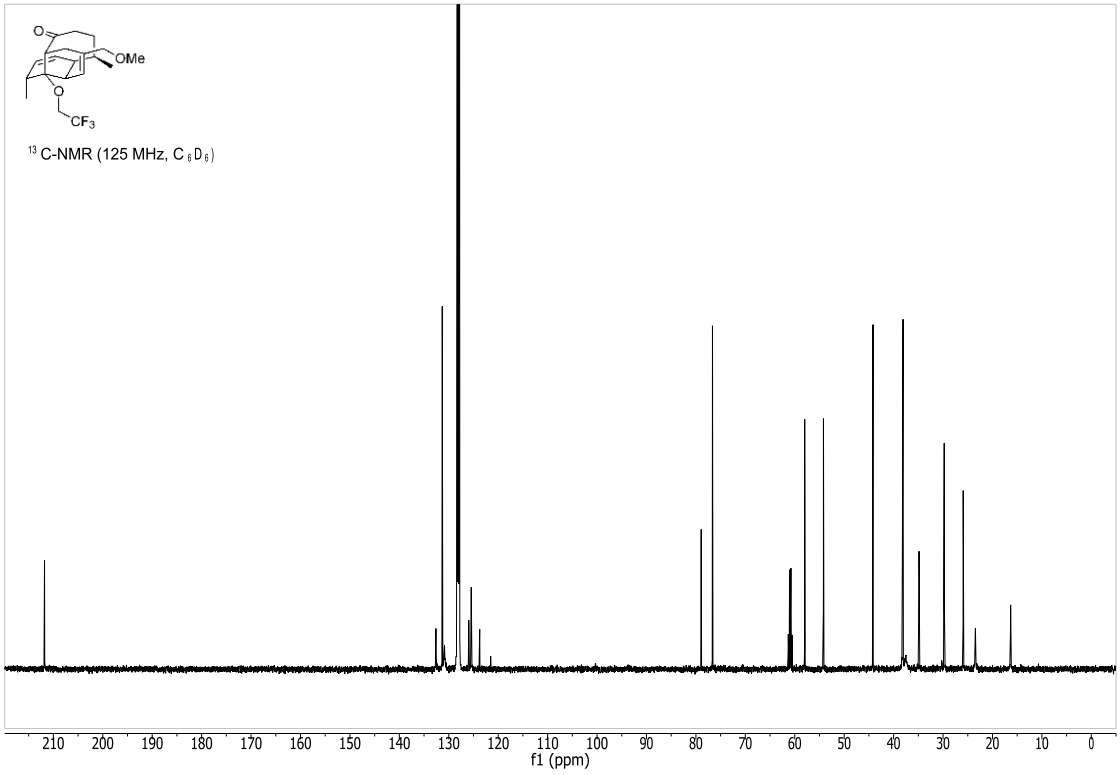

HO
OMe
OH
O
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

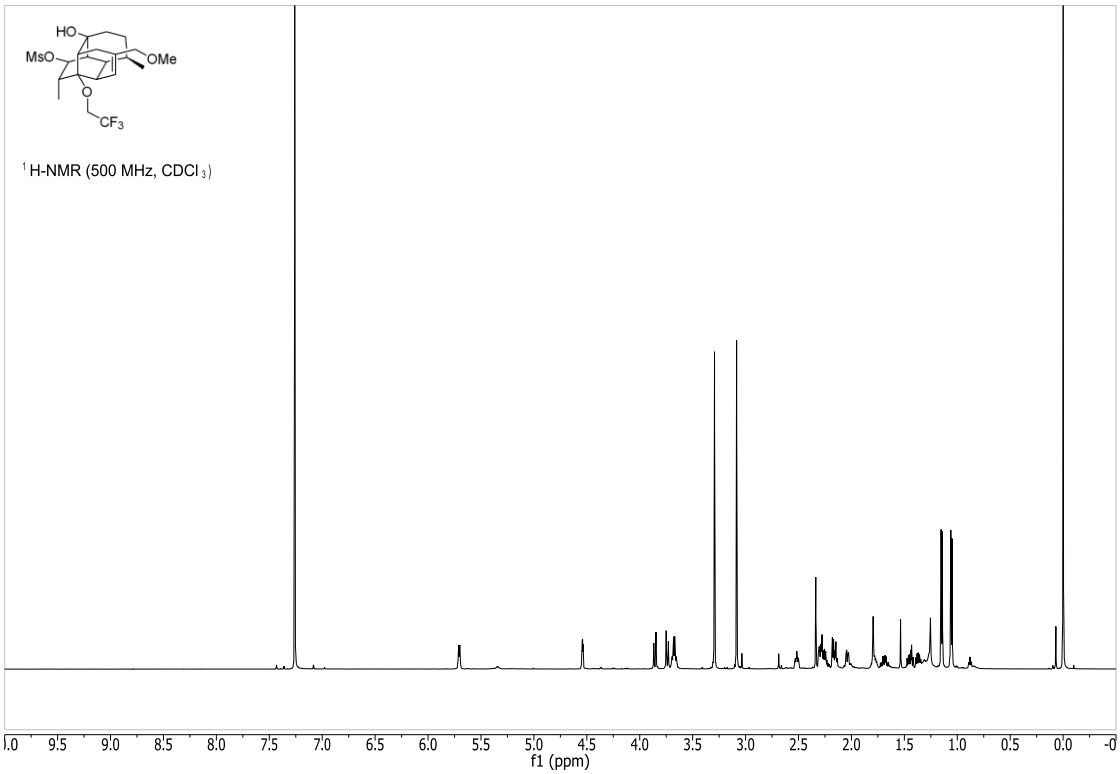

HO
OMe
OH
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

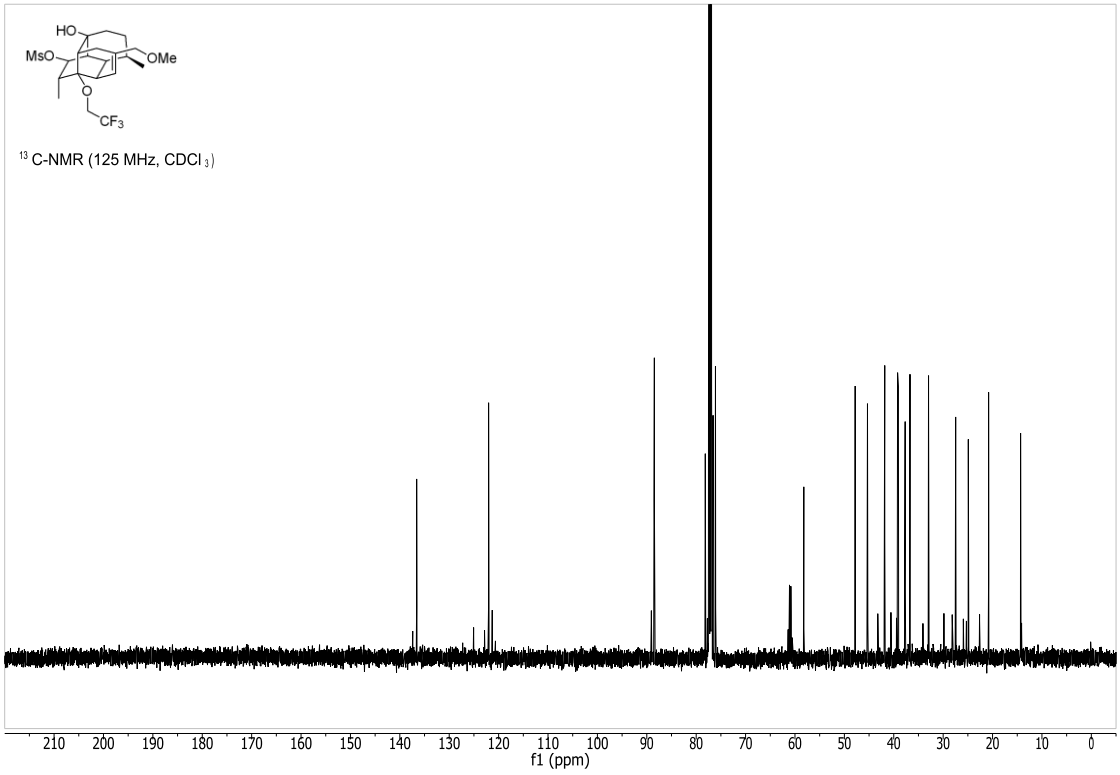

HO
OMe
O
O
Ms
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

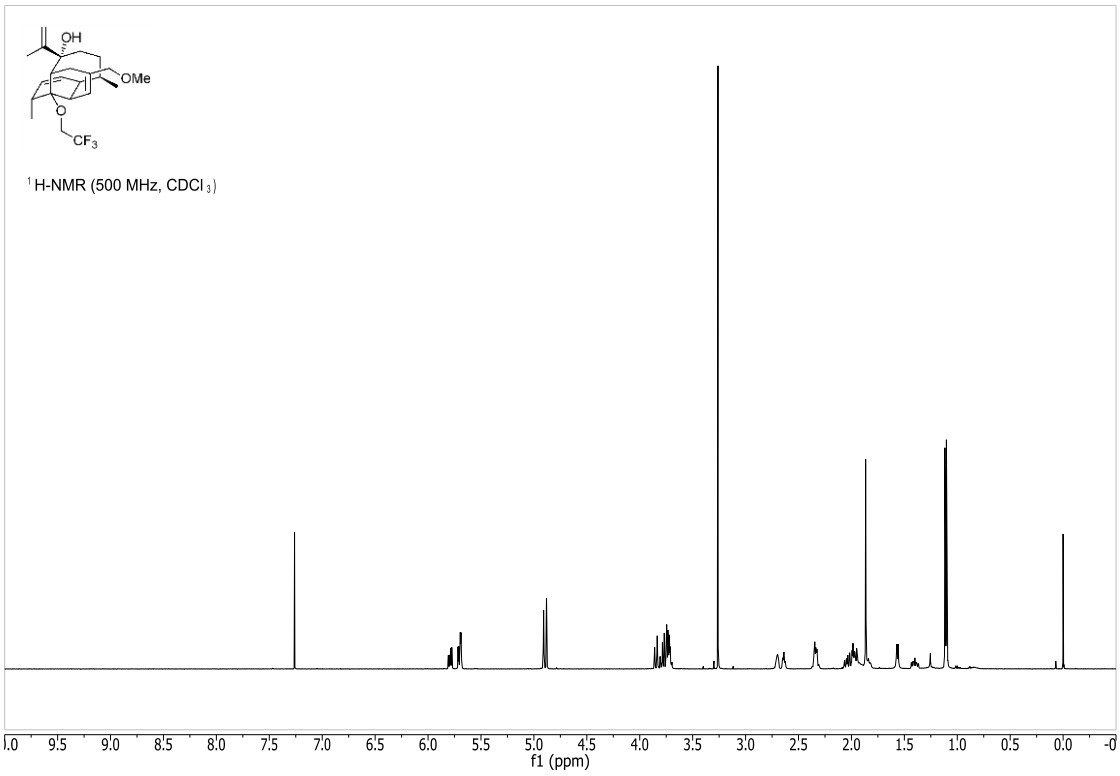

HO
OMe
O
O
Ms
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

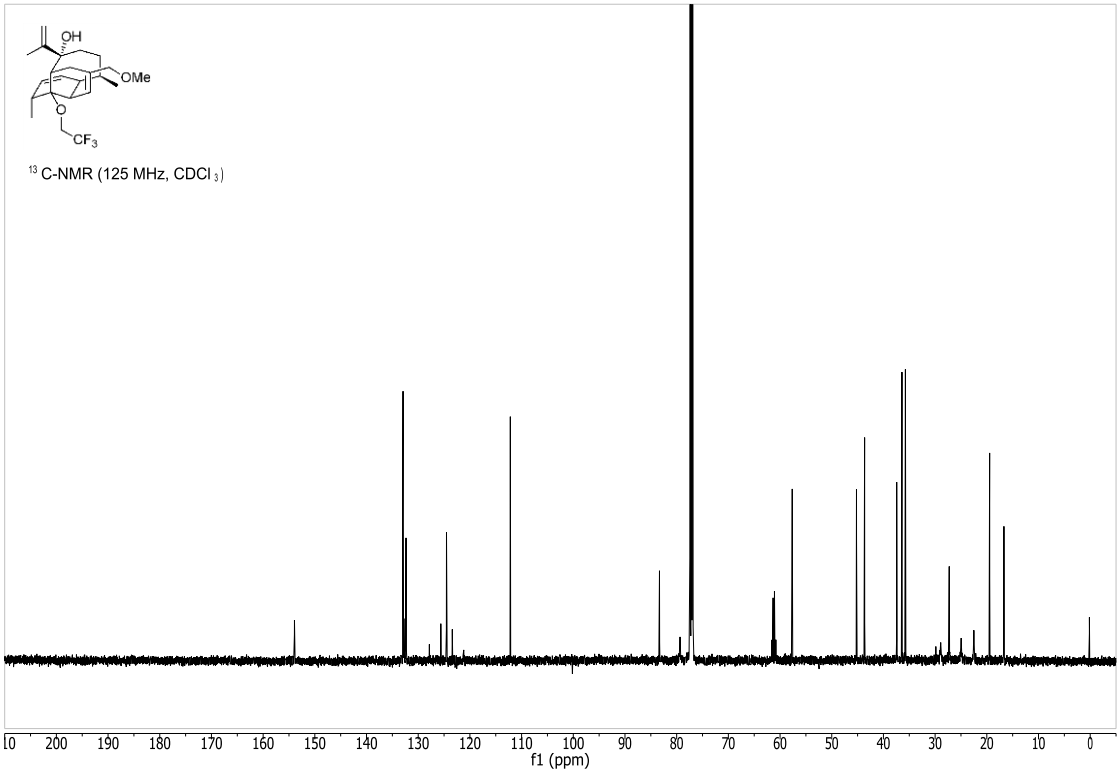

O
OMe
O
CF3
1 H-NMR (500 MHz, CDCl 3)
1.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

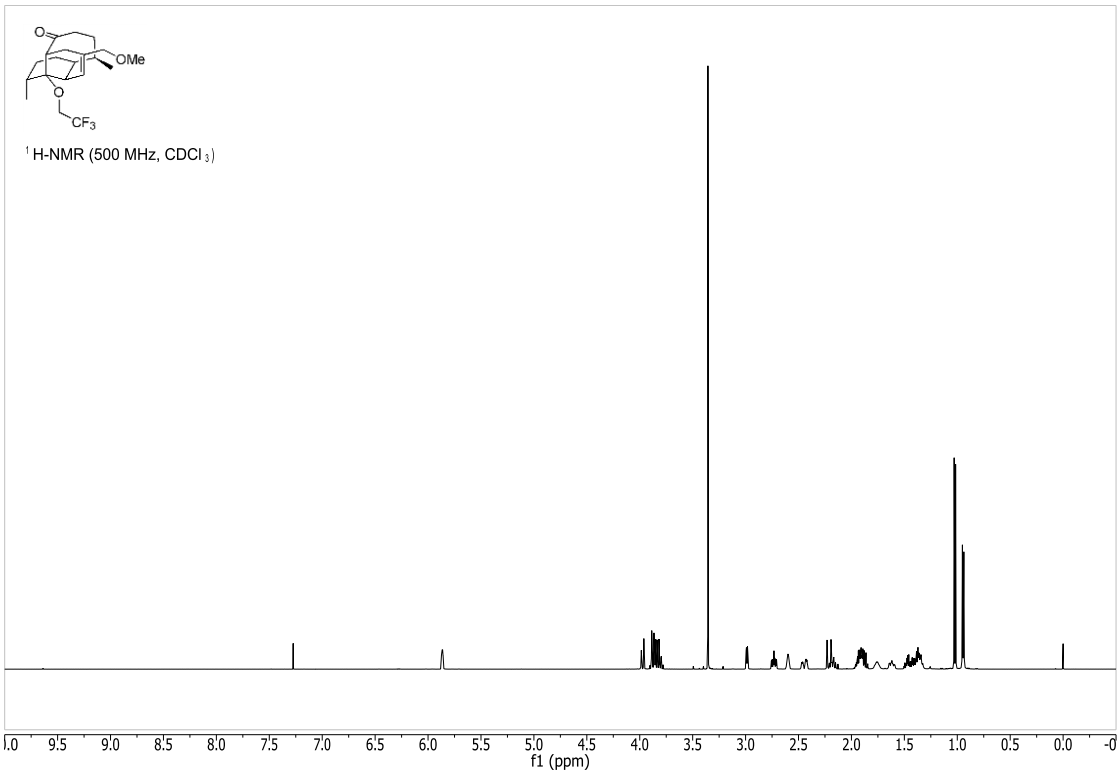

O
OMe
O
CF3
13 C-NMR (125 MHz, C 6 D 6)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

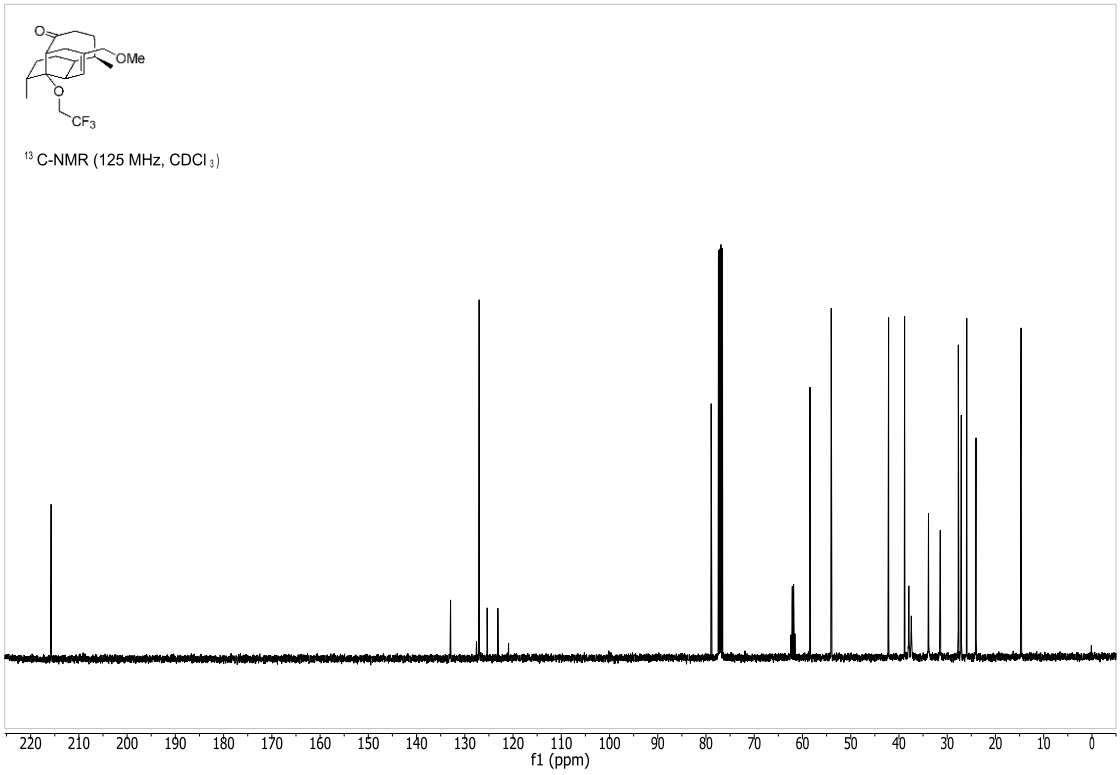

HO
MsO
OMe
O
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

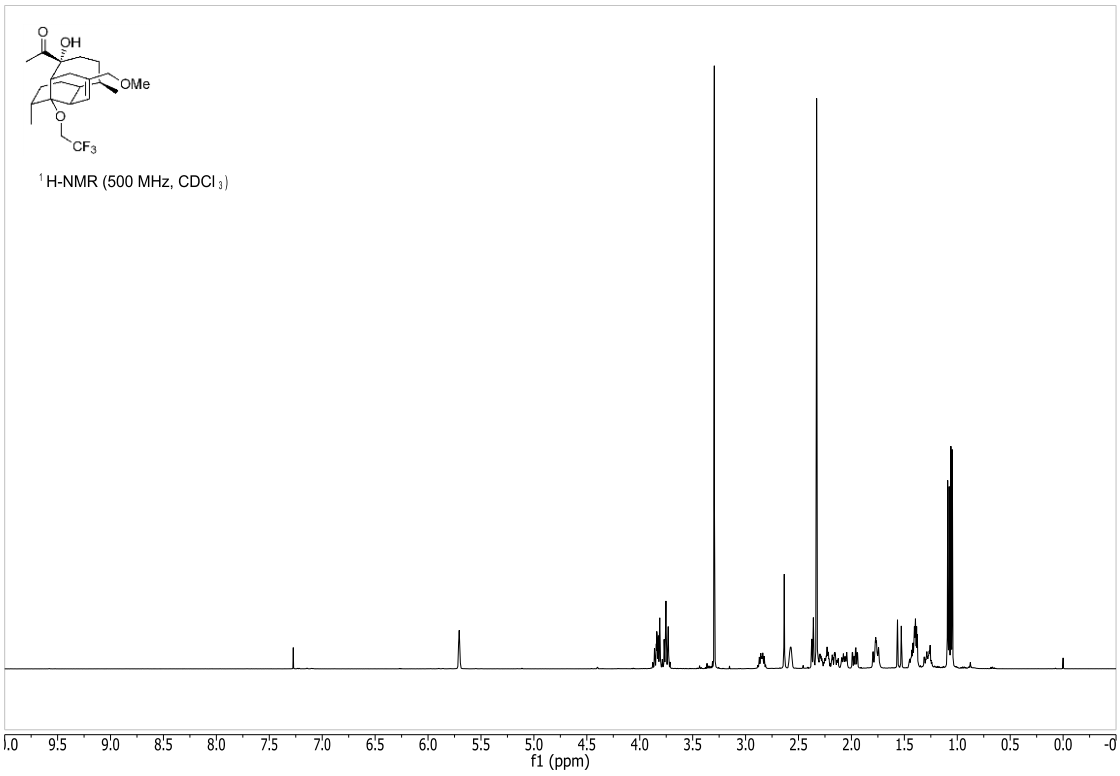

HO
MsO
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

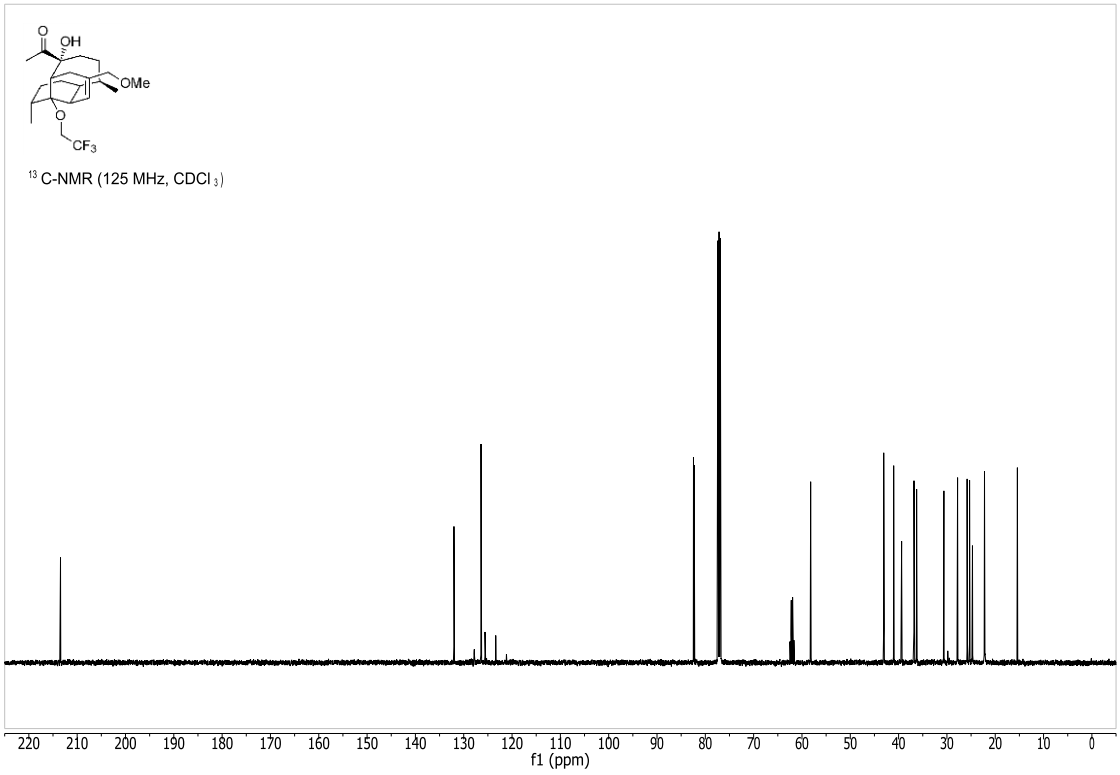

OH
OMe
O
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

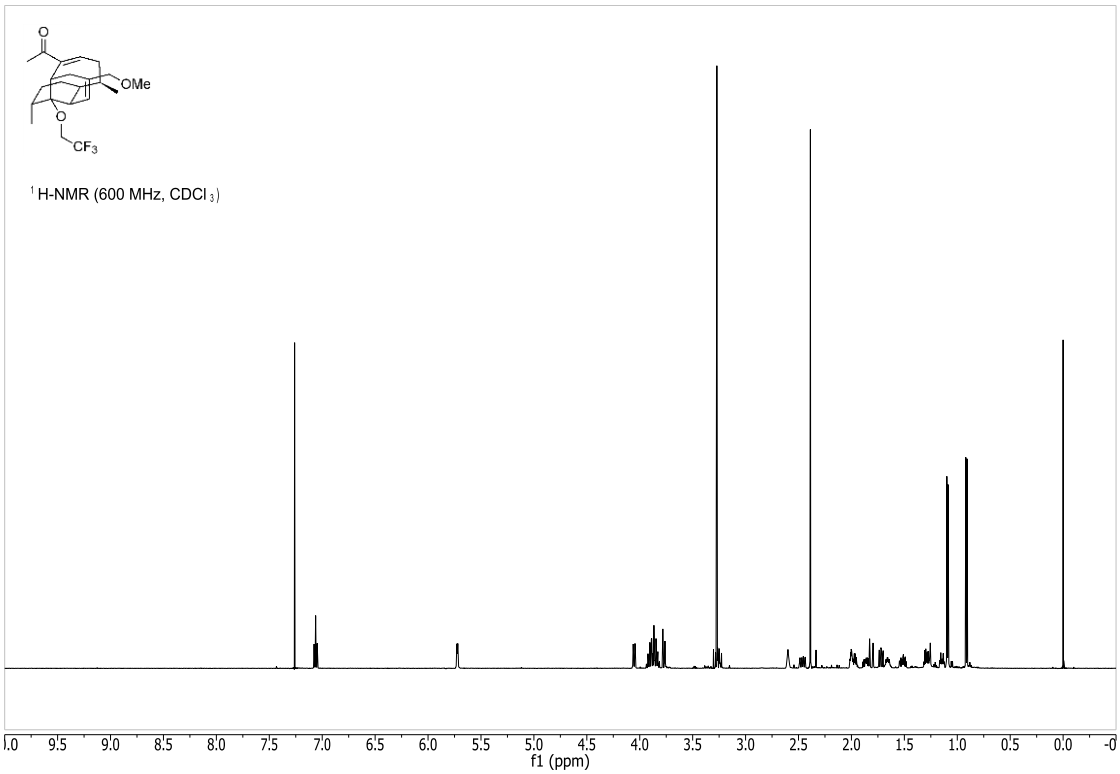

OH
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

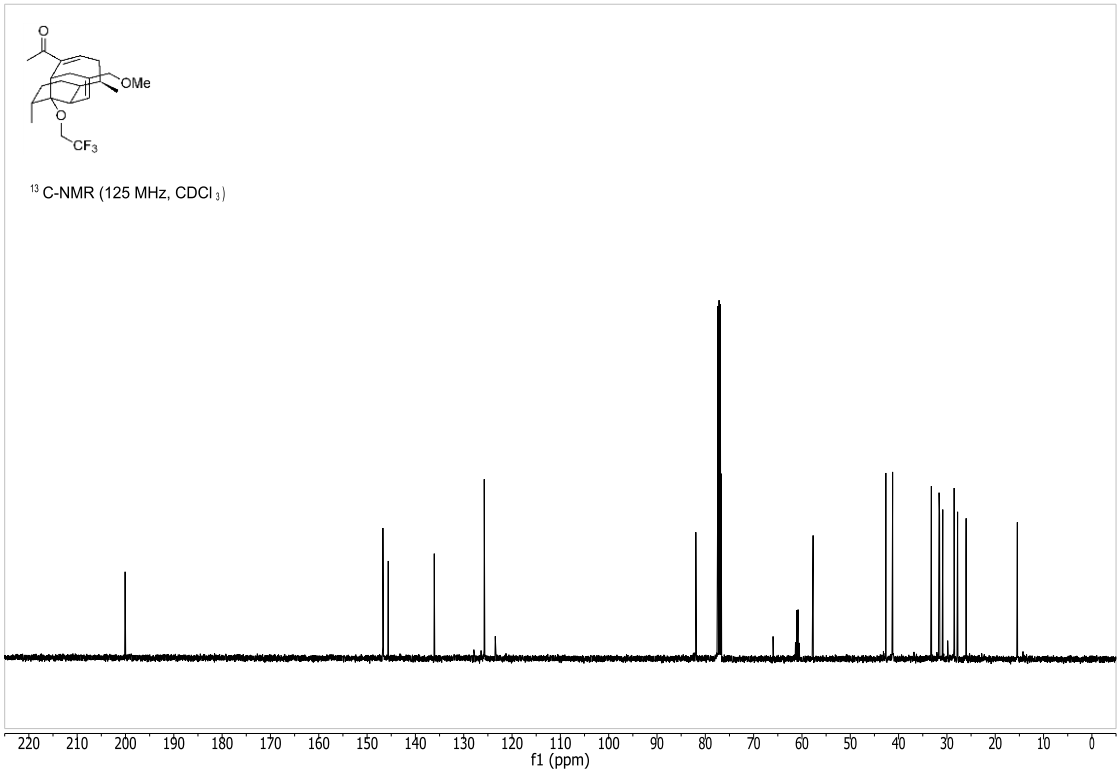

O
OMe
O
CF3
1 H-NMR (500 MHz, CDCl 3)
1.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

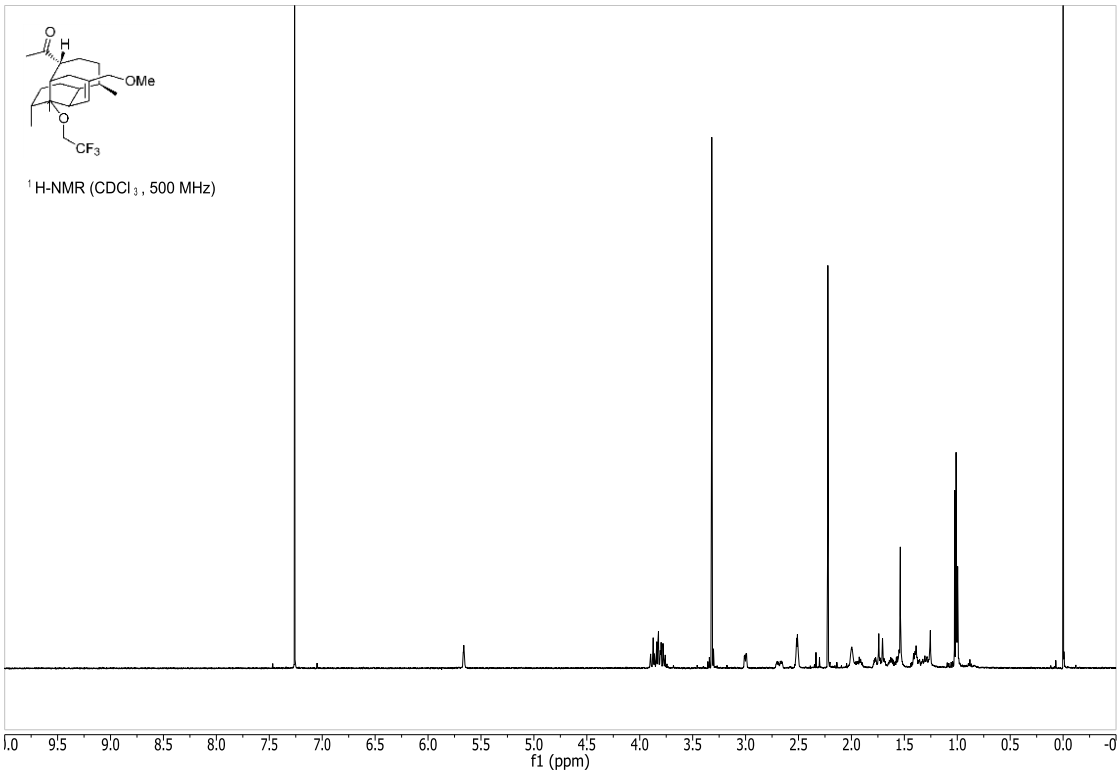

O
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

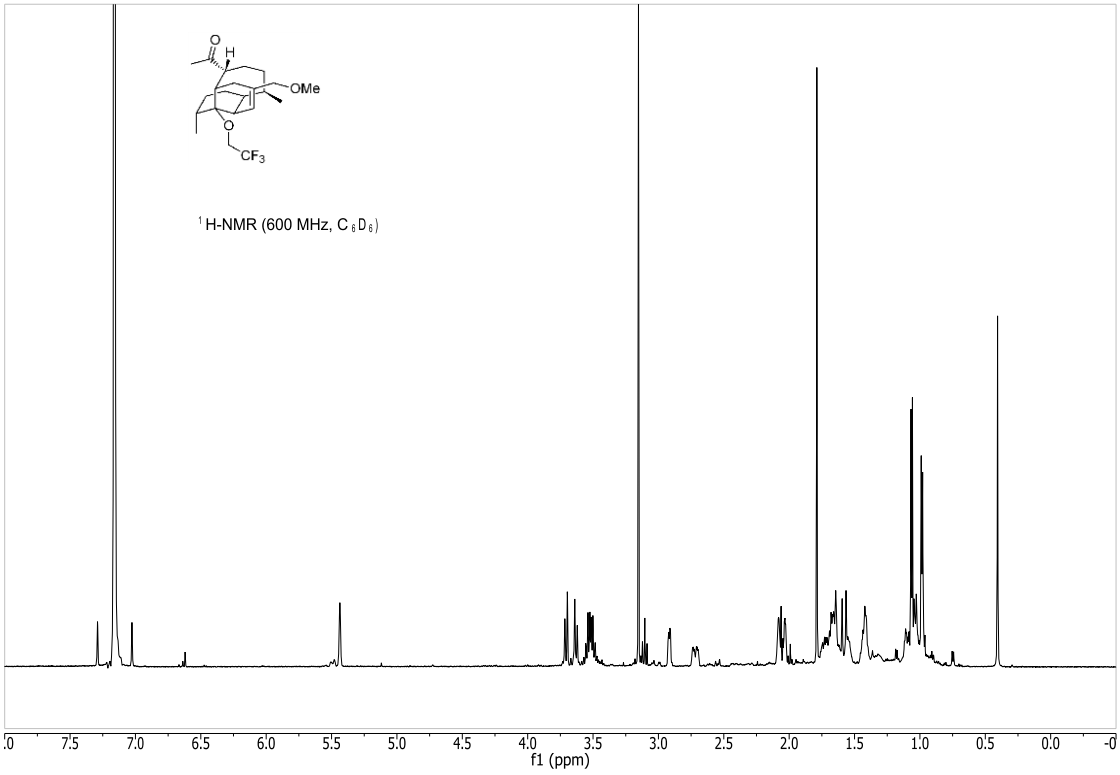

O
OH
OMe
O
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

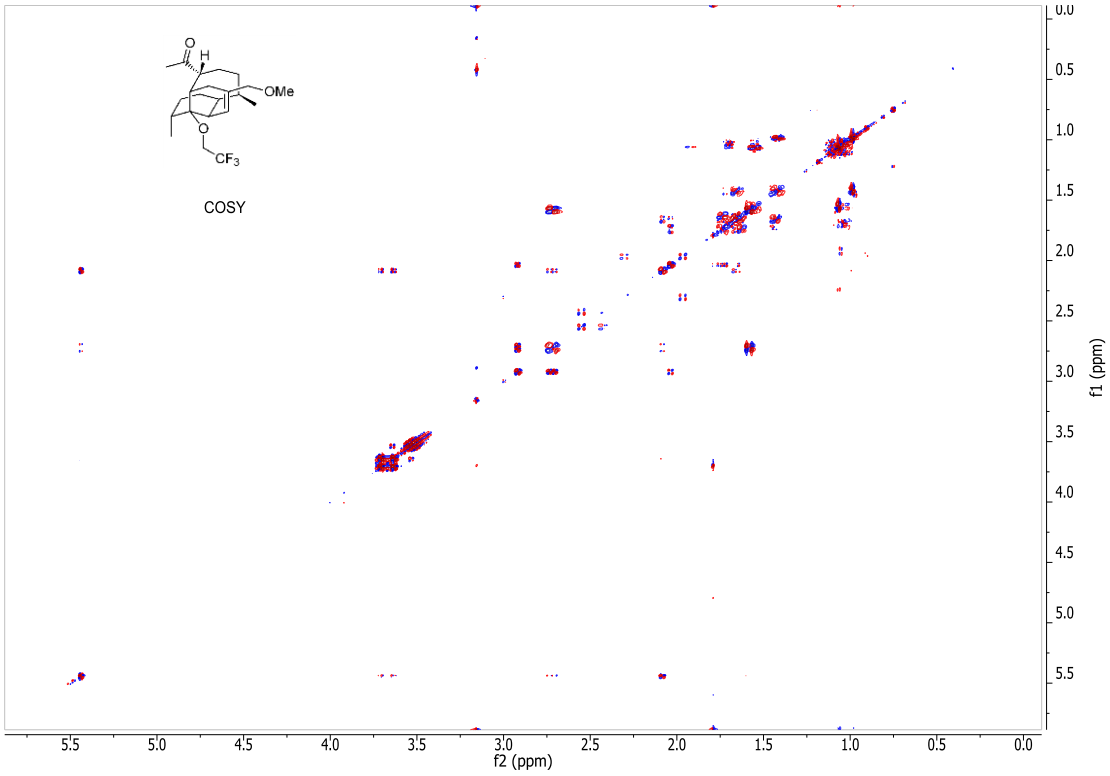

O
OH
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

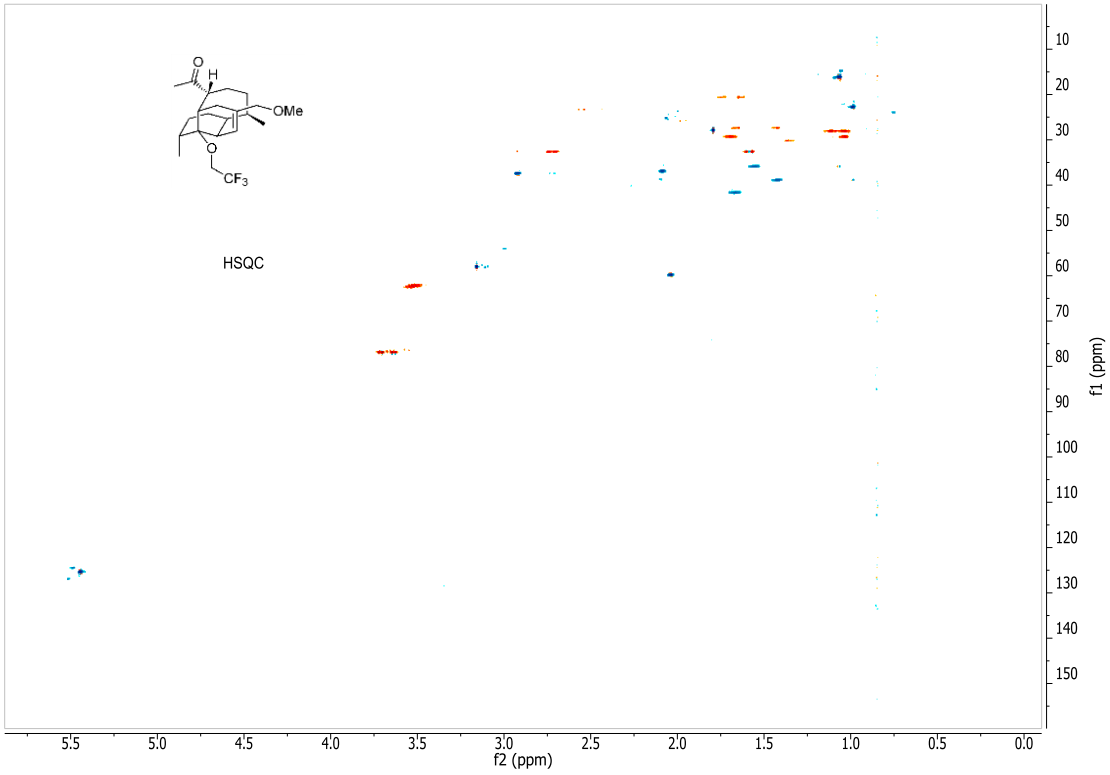

O
OMe
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

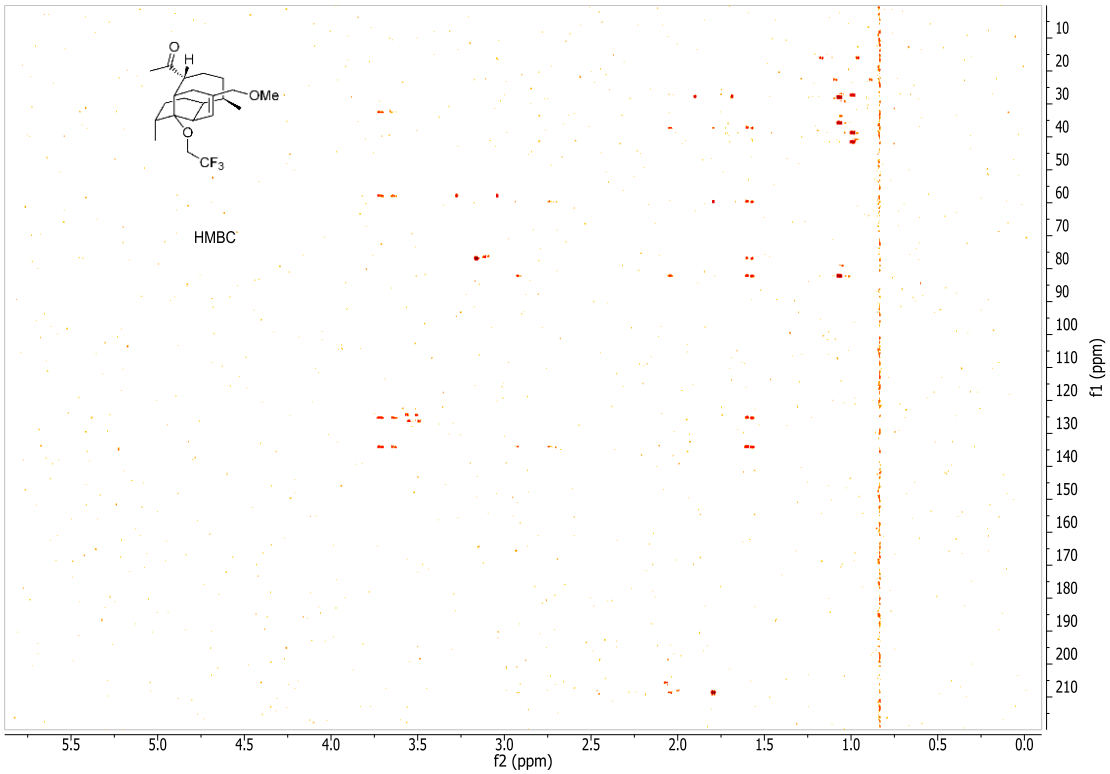

O
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)


OMe
CF3
1H-NMR (CDCl3, 500 MHz)
f1 (ppm)


OMe
CF3
1H-NMR (600 MHz, C6D6)
f1 (ppm)


O
H
OMe
O
CF3
COSY
f1 (ppm)
f2 (ppm)


O
H
OMe
O
CF3
HSQC
f1 (ppm)
f2 (ppm)


HMBC
OMe
CF3
f2 (ppm)
f1 (ppm)

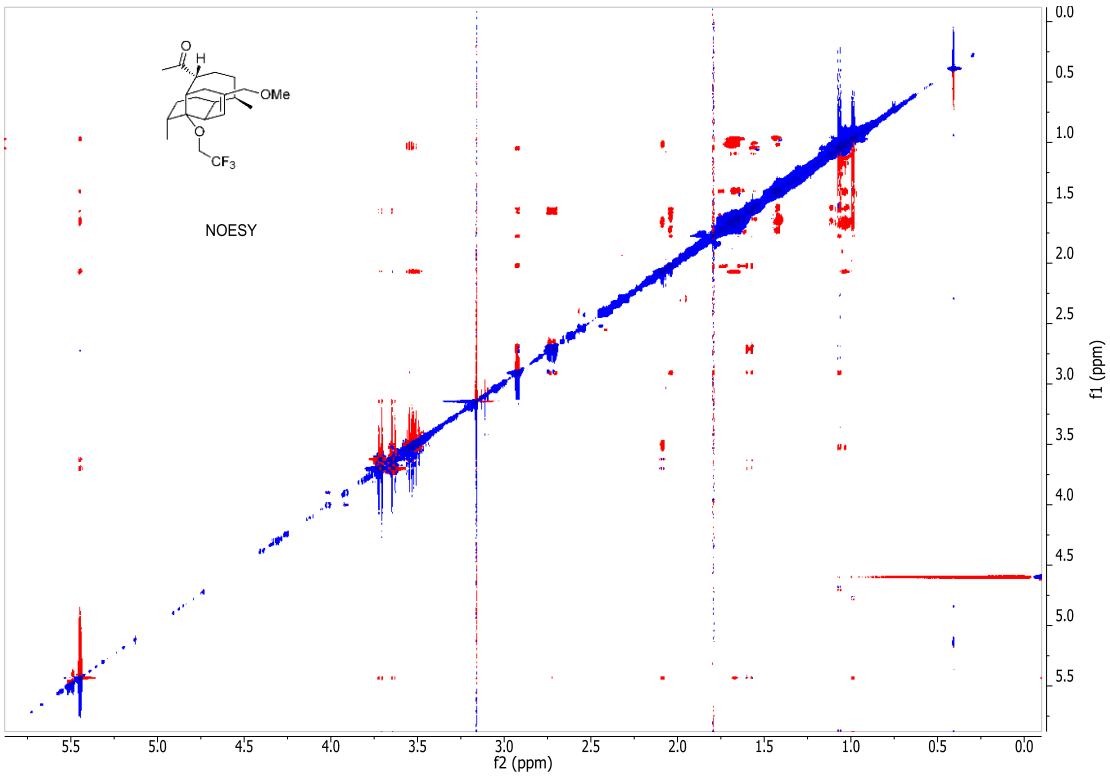
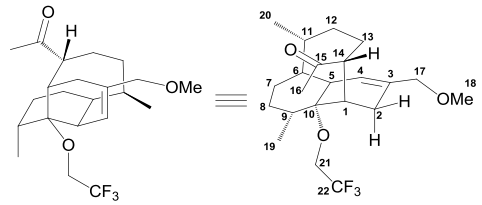
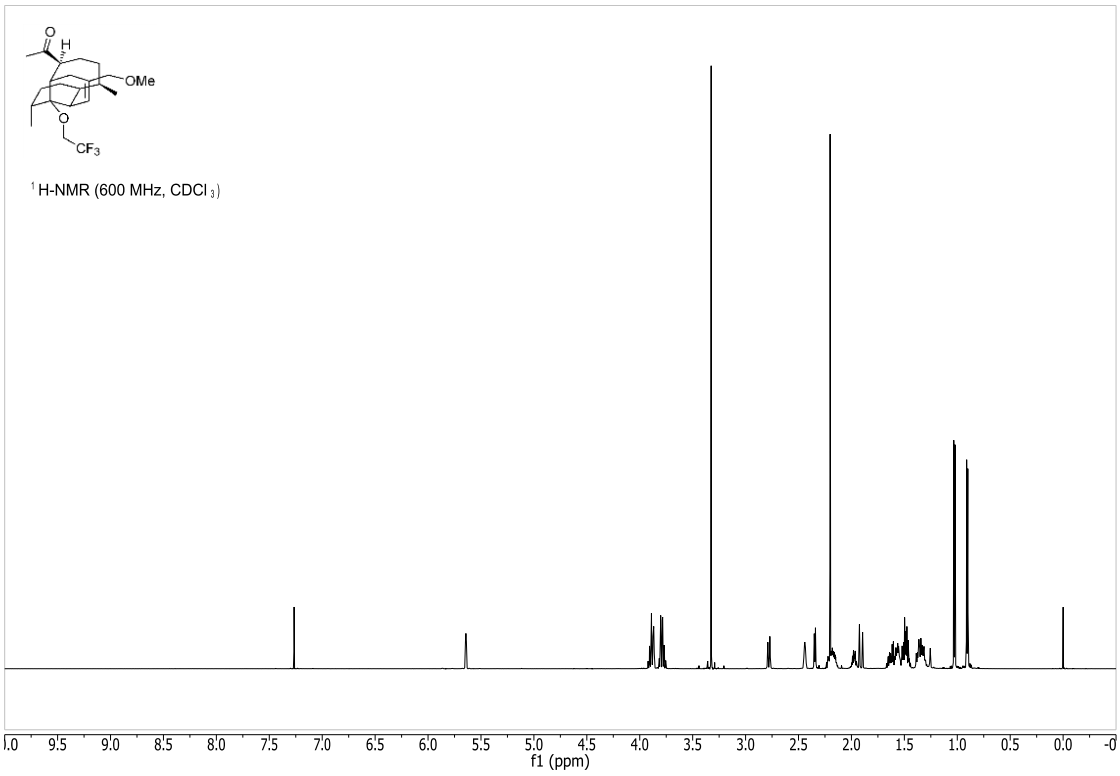
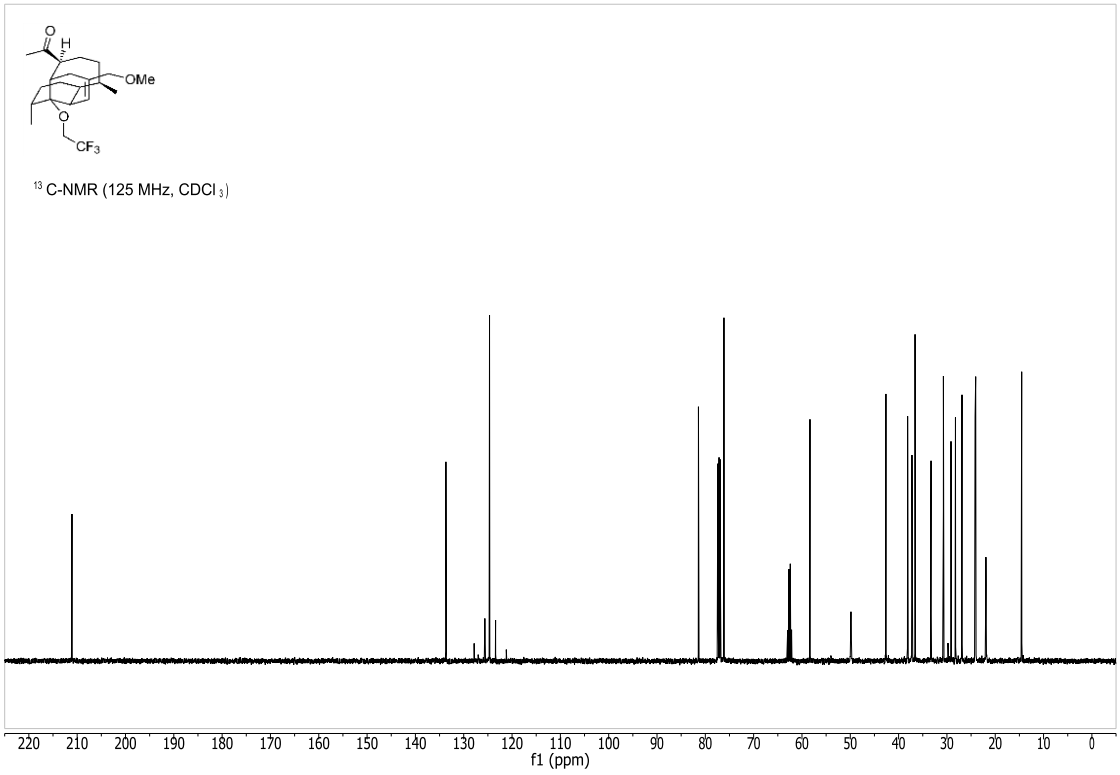

NOESY
OMe
CF3
f2 (ppm)
f1 (ppm)

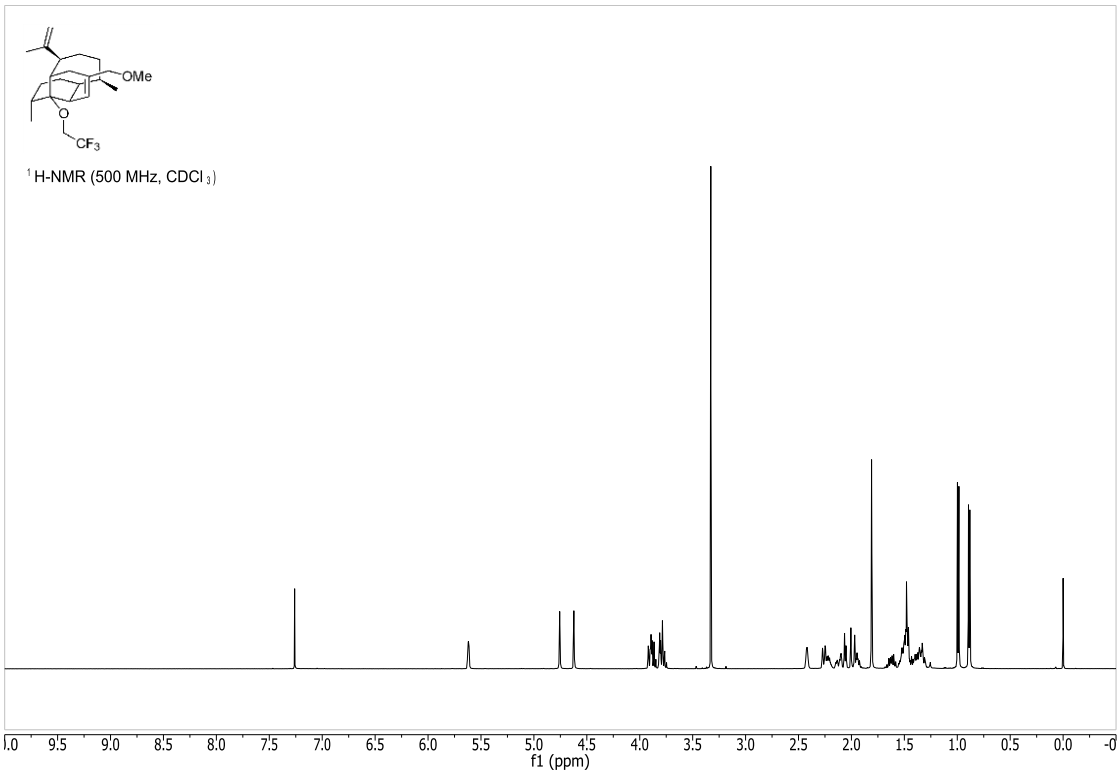
Table A3.4. 2D-NMR Data of Compound **4.37**

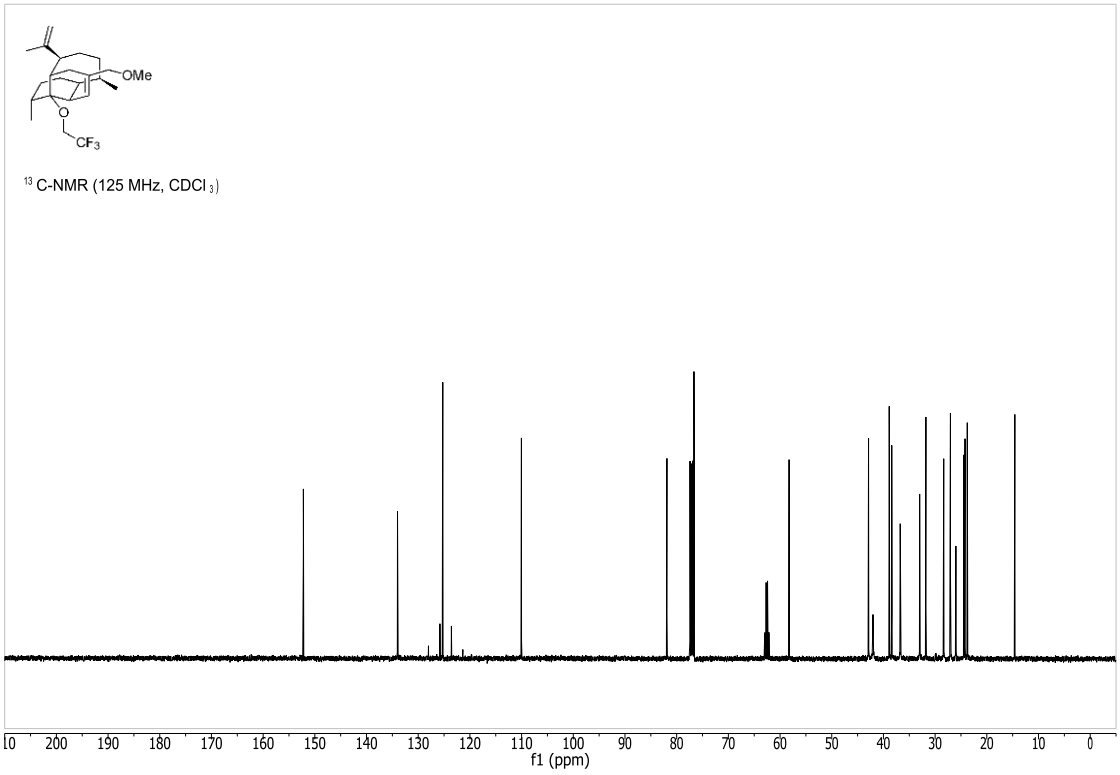


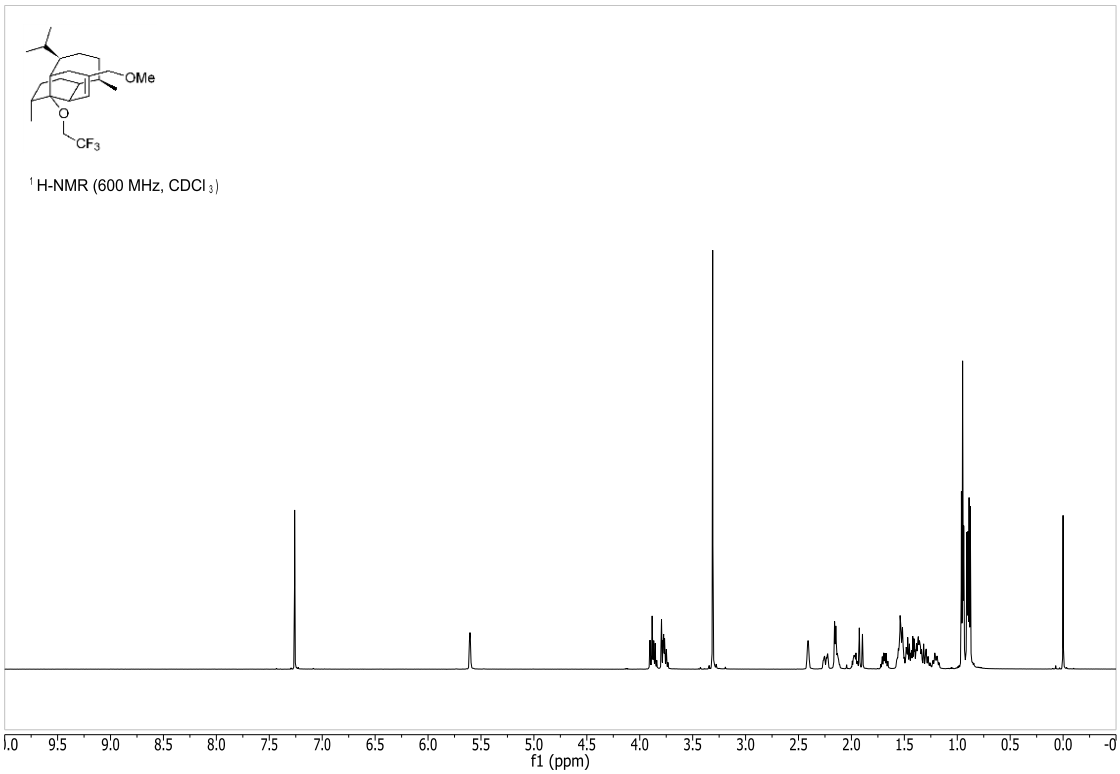
Position	δ 13C (ppm)	δ 1H (ppm)	Type	COSY correlations	HMBC correlations	ROESY correlations
1	37.54	2.92	CH	H-2, H-14	C-3, C-10	H-14, H-16, H-2a, H-19
2a	32.83	1.58	CH_2	H-2b	C-3, C-4, C-10, C-17, C-14, C-5	H-17a, H-17b, H-1, H-2b, H-14
2b		2.72		H-4, H-1, H-5, H-2a	C-3, C-14	H-2a
3	134.38		Cq			
4	125.35	5.44	CH	H-17a, H-17b, H-2b, H-5		H-17a, H-17b, H-5, H-6, H-12a, H-13a
5	37.05	2.08	CH	H-4, H-17a, H-17b, H-2b, H-6		H-4, H-21b, H-6, H-7, H-8
6	41.78	1.66	CH			H-4, H-5, H-12a, H-7a, H-20
7a	29.64	1.02	CH_2	H-8b, H-7b		
7b		1.68		H-8a, H-7a		
8a	28.23	1.04	CH_2	H-9, H-7b, H-8b		
8b		1.11		H-8a		H-9, H-7b
9	36.04	1.55	CH	H8a		
10	82.38		Cq			
11	39.07	1.42	CH	H-20		H-9
12a	27.63	1.43	CH_2	H-12b, H-13b		H-13b, H-12b
12b		1.66		H-12a		
13a	20.82	1.62	CH_2	H-13b		
13b		1.74		H-14, H-13a, H-12a		H-14, H-12a
14	59.97	2.04	CH	H-1, H-13a, H-13b	C-15, C-10, C-1	H-1, H-13b, H-13a, H-2a
15	208.61		Cq			
16	28.00	1.79	CH_3		C-14, C-15	
17a	77.04	3.63	CH_2	H-4, H-5	C-3, C-4, C-18, C-2	H-4, H-18, H-2a
17b		3.71		H-4, H-5	C-3, C-4, C-18, C-2	H-4, H-18, H-2a
18	58.18	3.15	CH_3		C-17	
19	16.41	1.06	CH_3	H-9	C-10, C-9, C-8	H-21b, H-1, H-16
20	22.91	0.99	CH_3	H-11	C-6, C-11, C-12	H-4
21a	62.48	3.49	CH_2			H-2b, H-5, H-8
21b		3.55				H-2b, H-5, H-8
22	125.63		Cq			

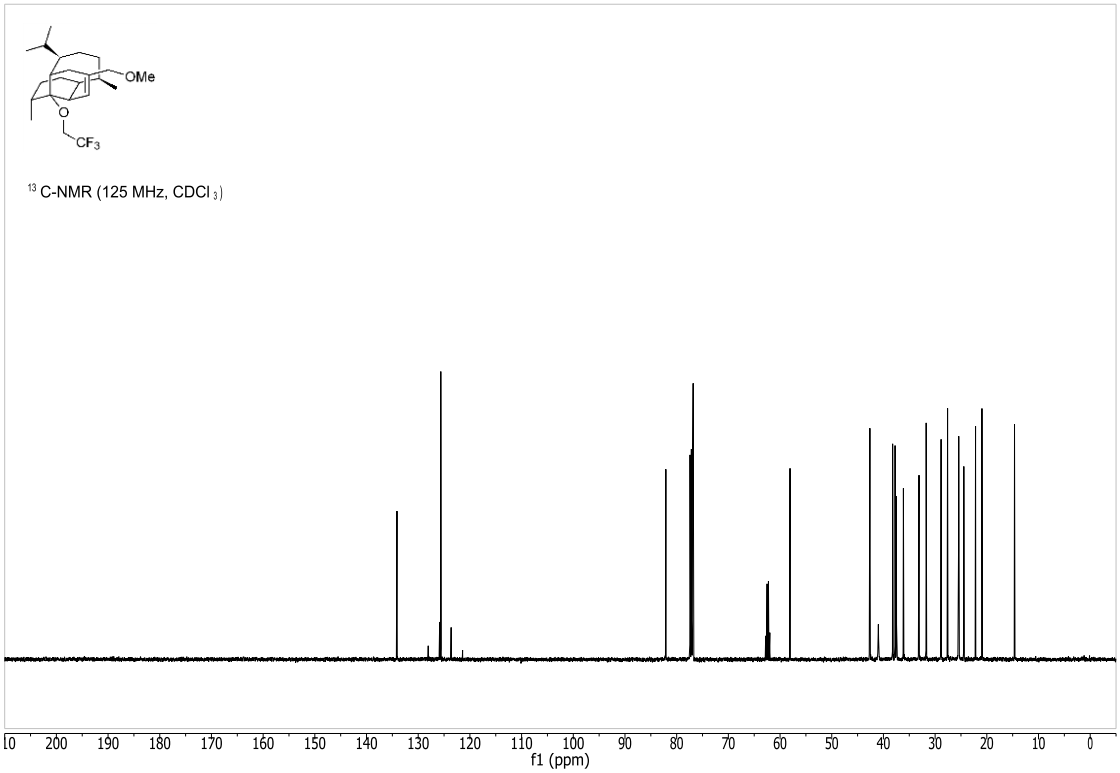

O
H
OMe
O
CF3
1 H-NMR (600 MHz, CDCl 3)
1.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)

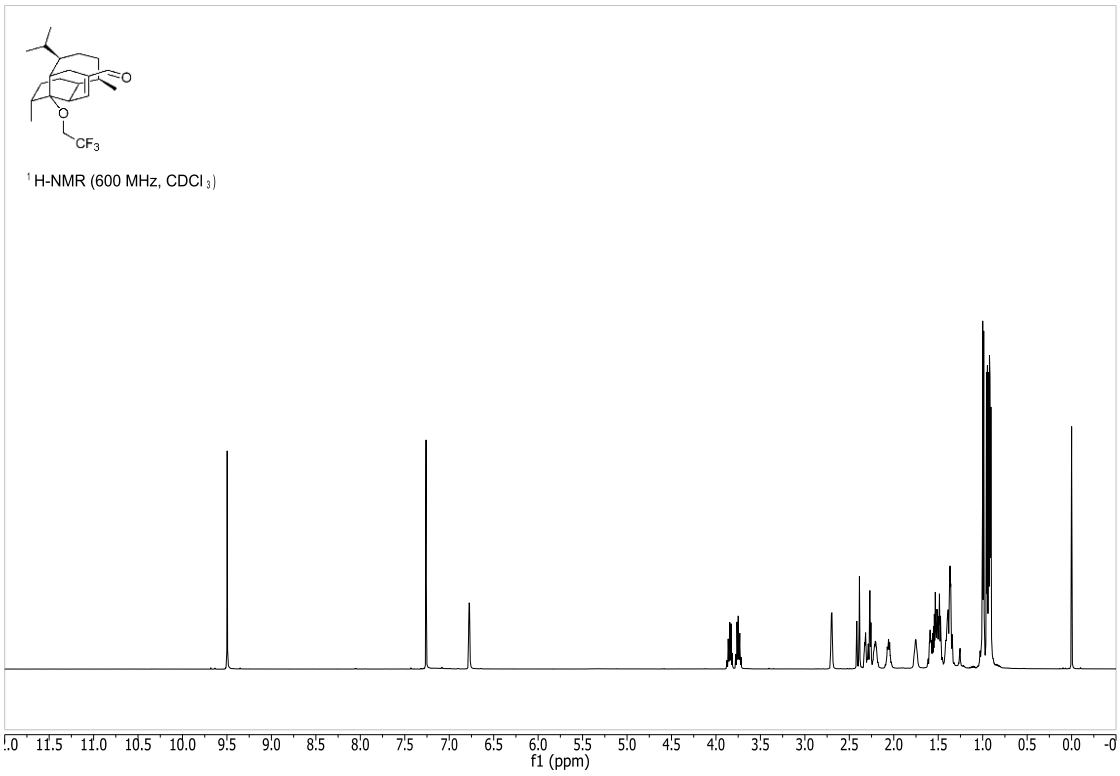

O
H
OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

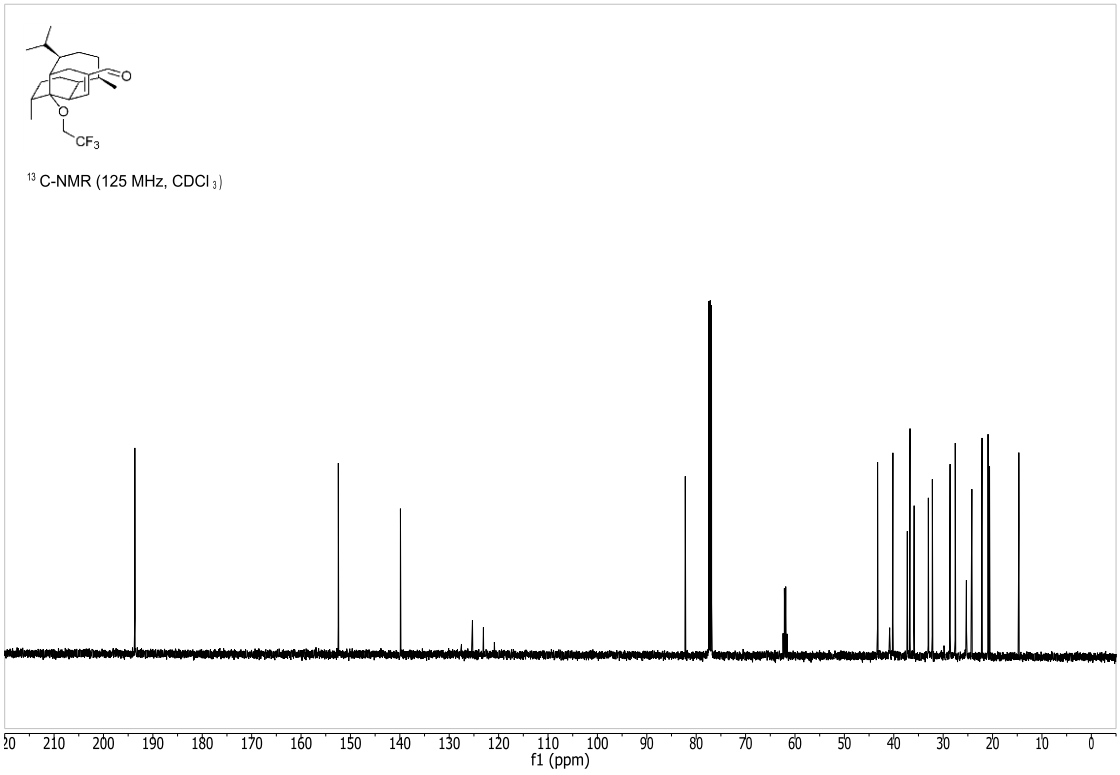

OMe
O
CF3
1 H-NMR (500 MHz, CDCl 3)
f1 (ppm)

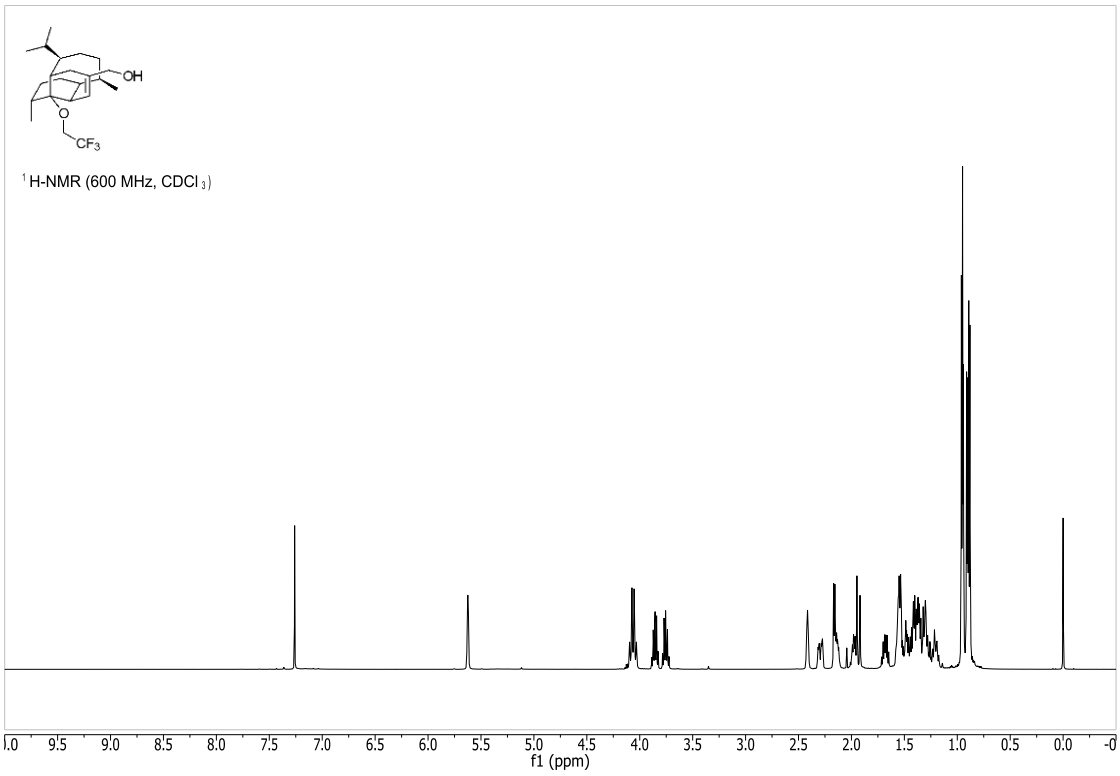

OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

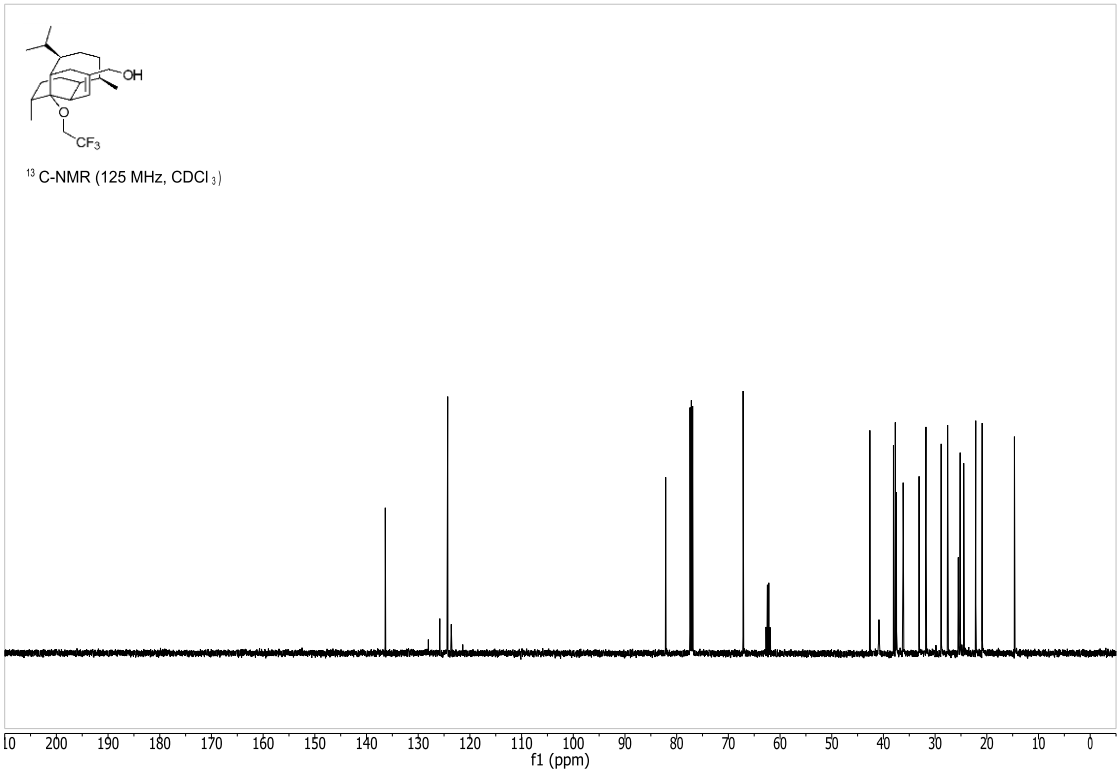

OMe
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

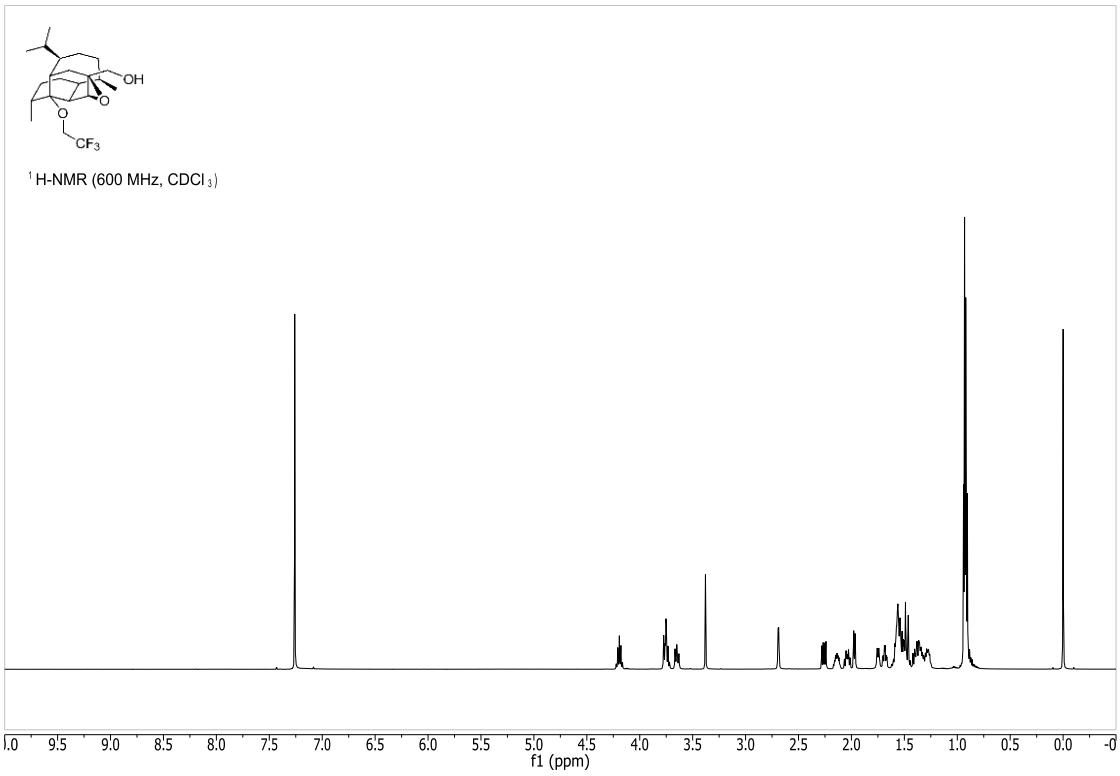

OMe
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

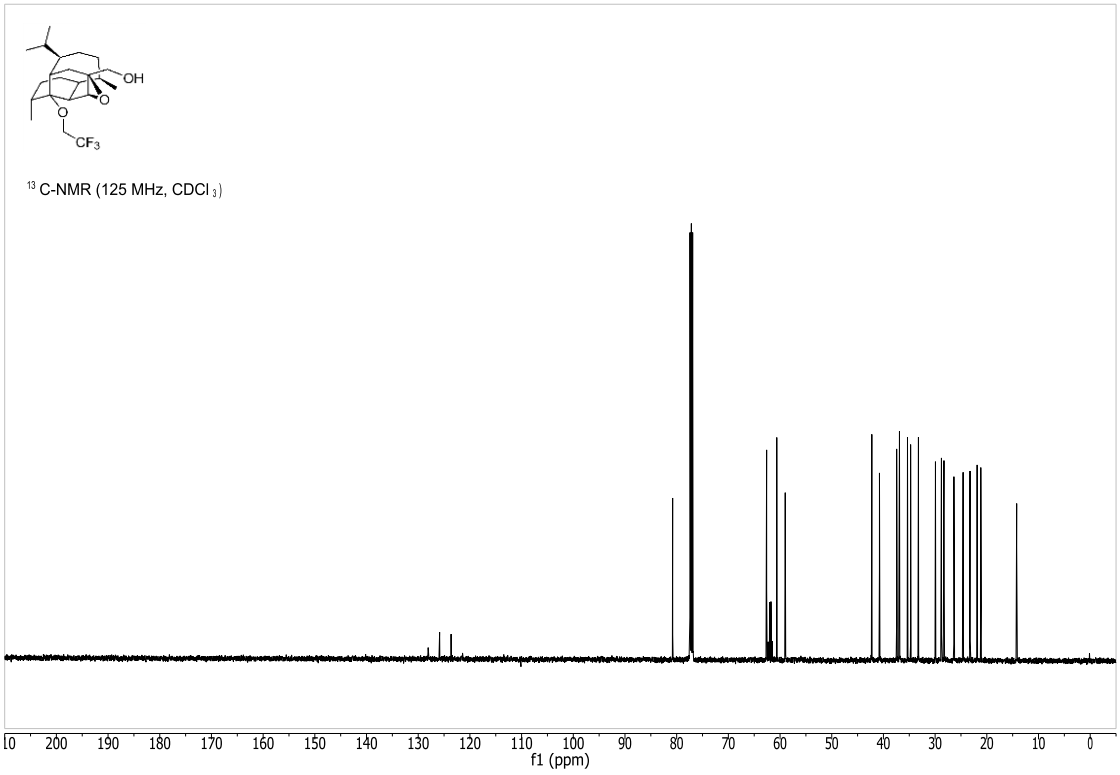

O
O
CF3
1 H-NMR (600 MHz, CDCl 3)
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

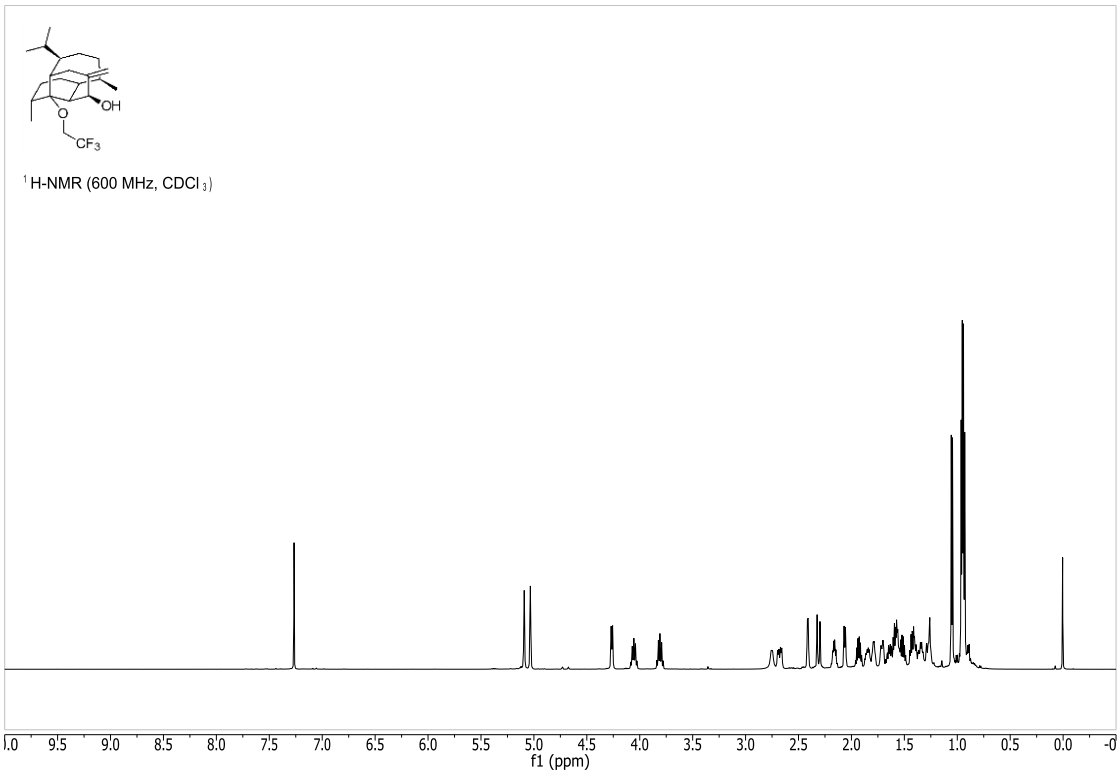

O
O
CF3
13 C-NMR (125 MHz, CDCl 3)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

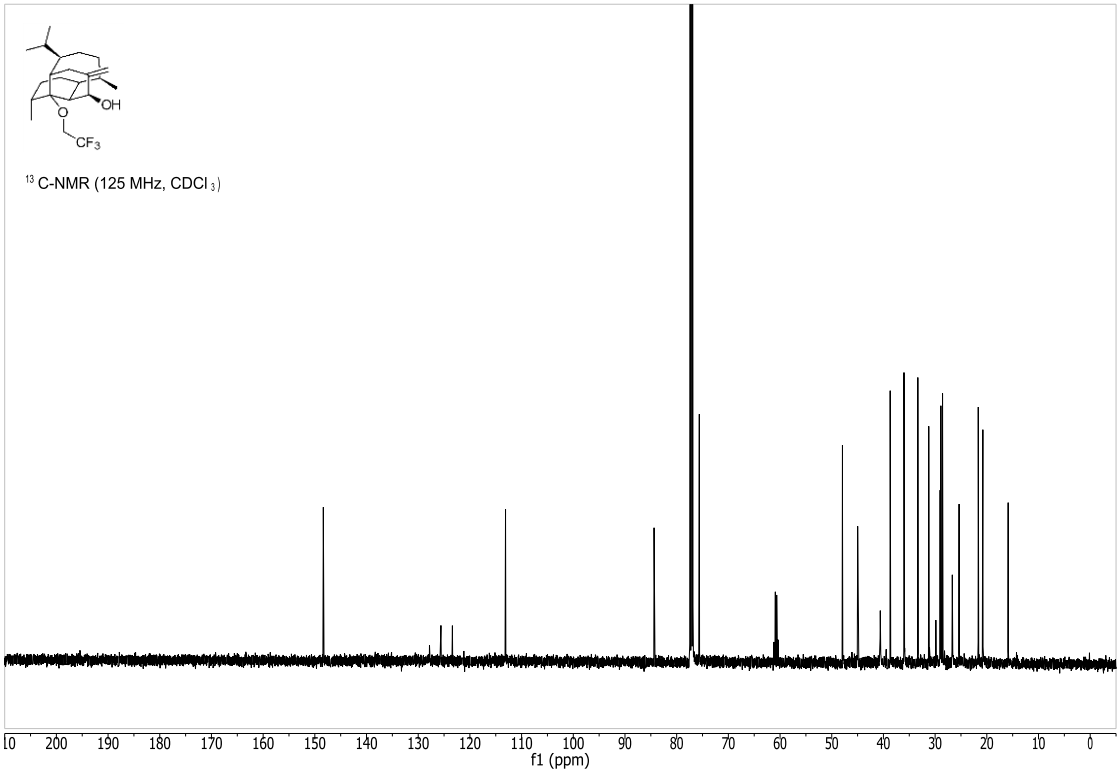

OH
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

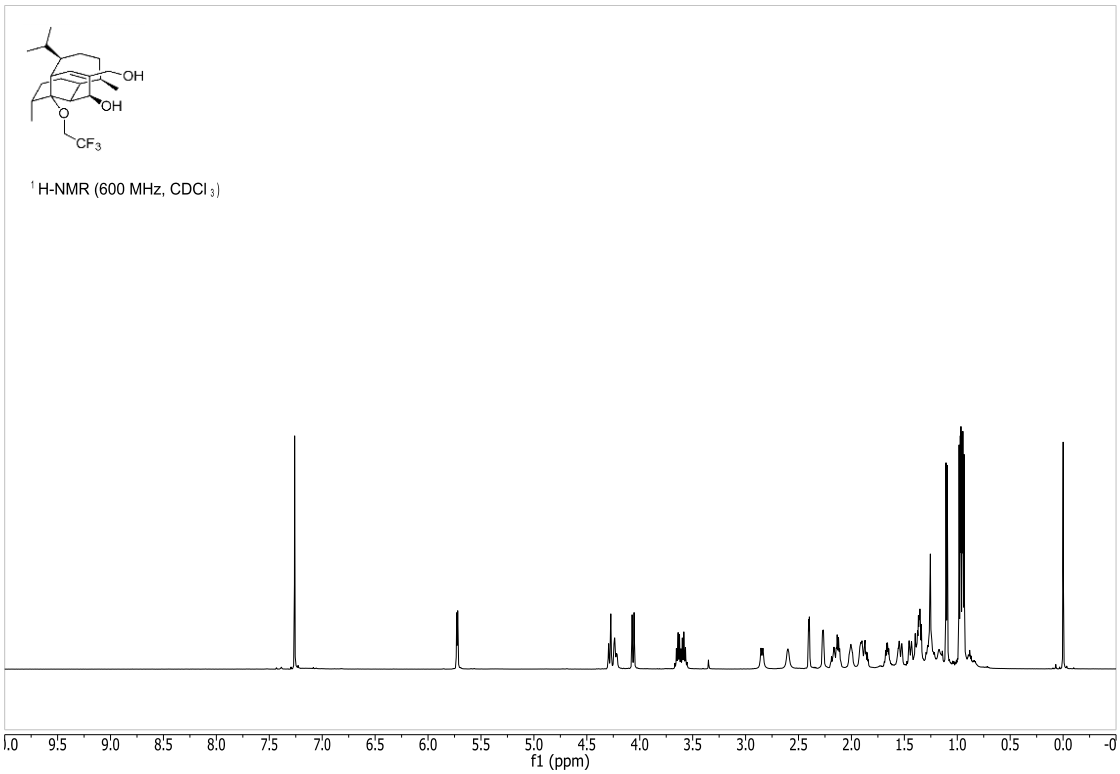

OH
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

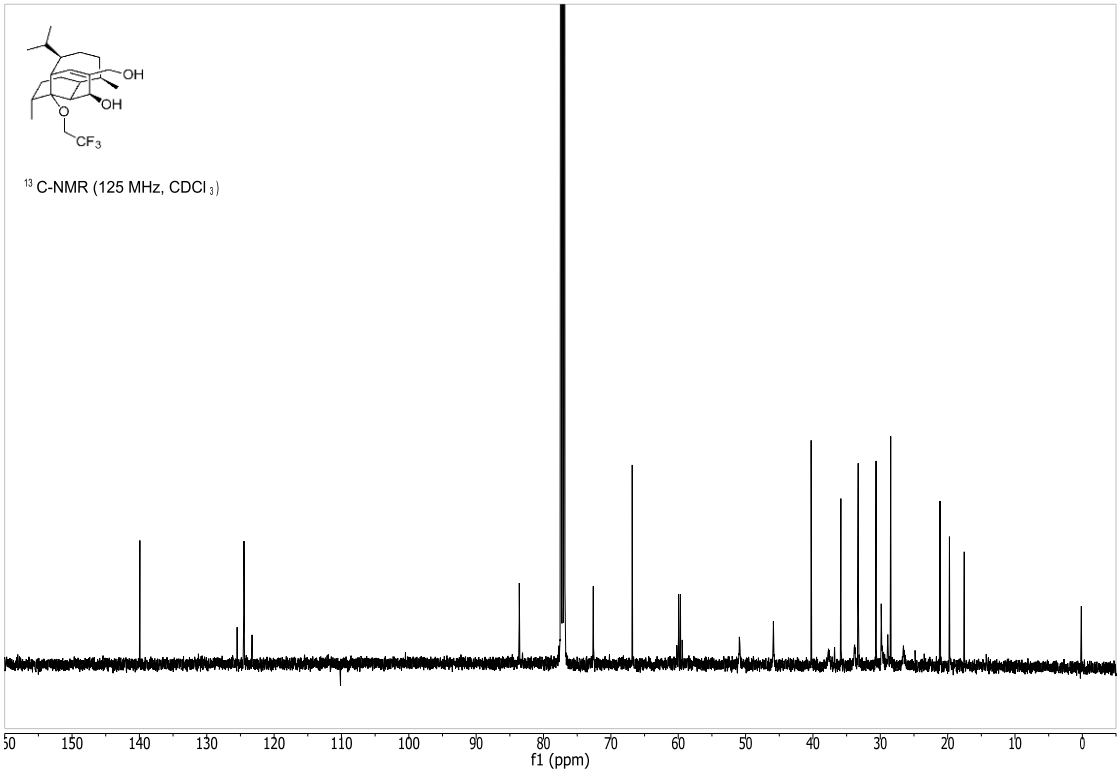

OH
O
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

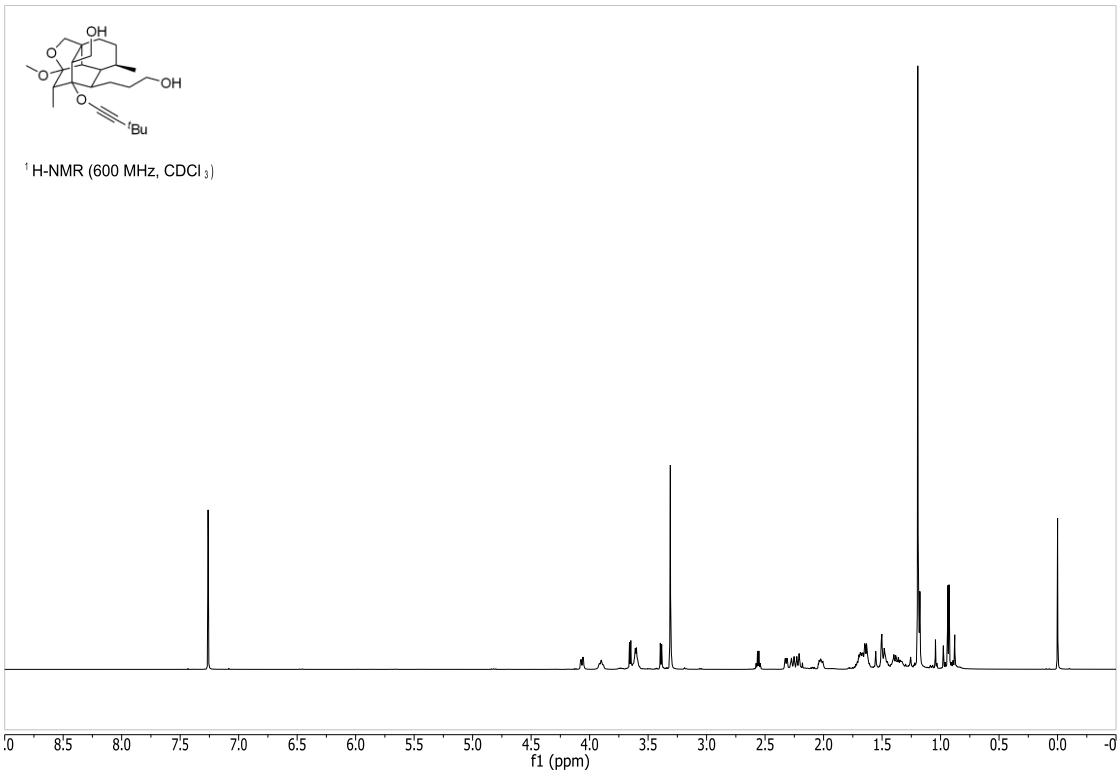

OH
O
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

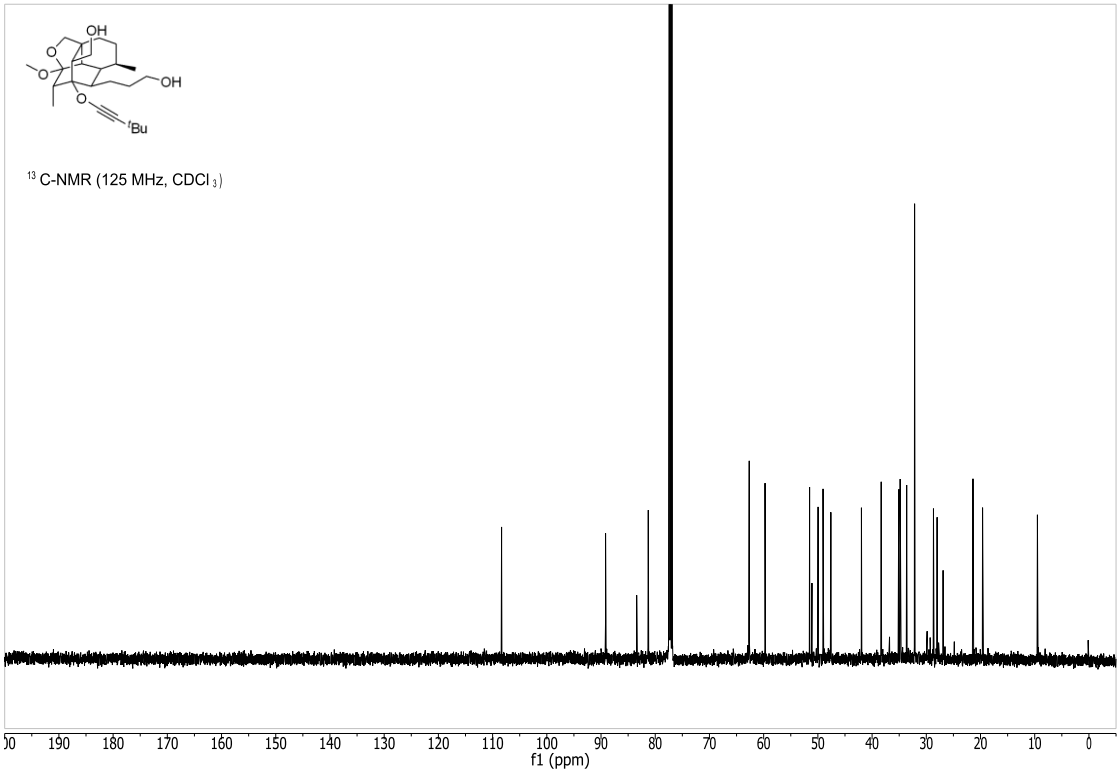

OH
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

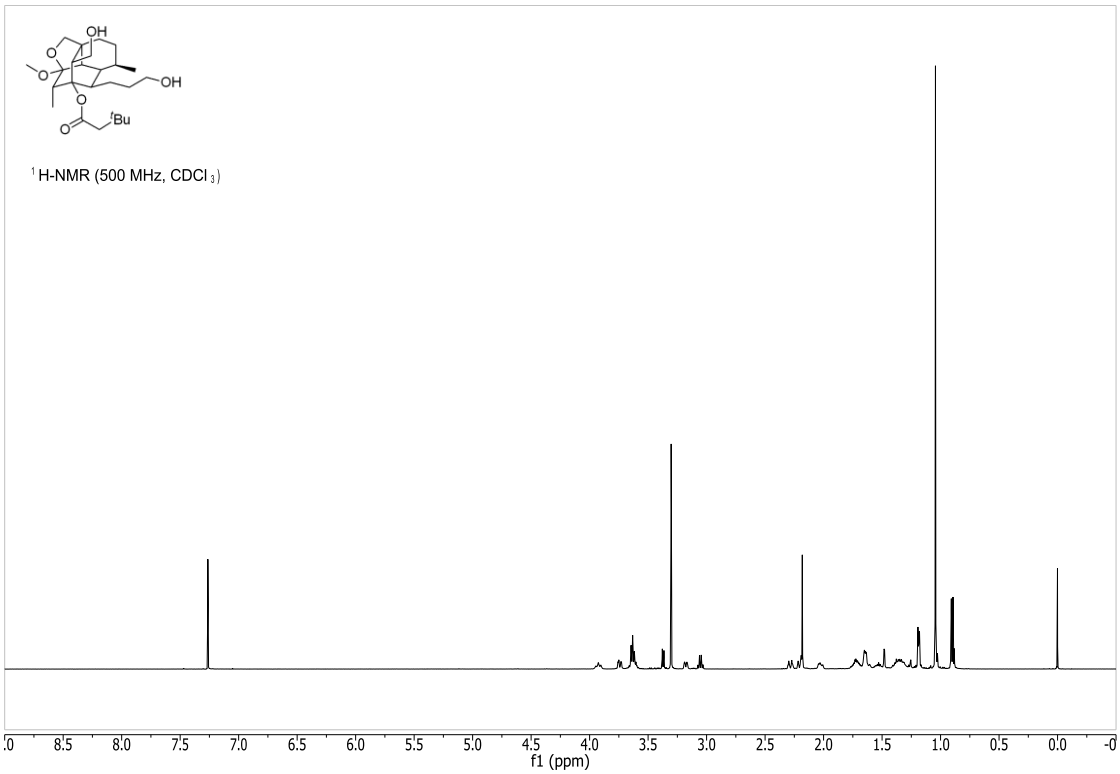

OH
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

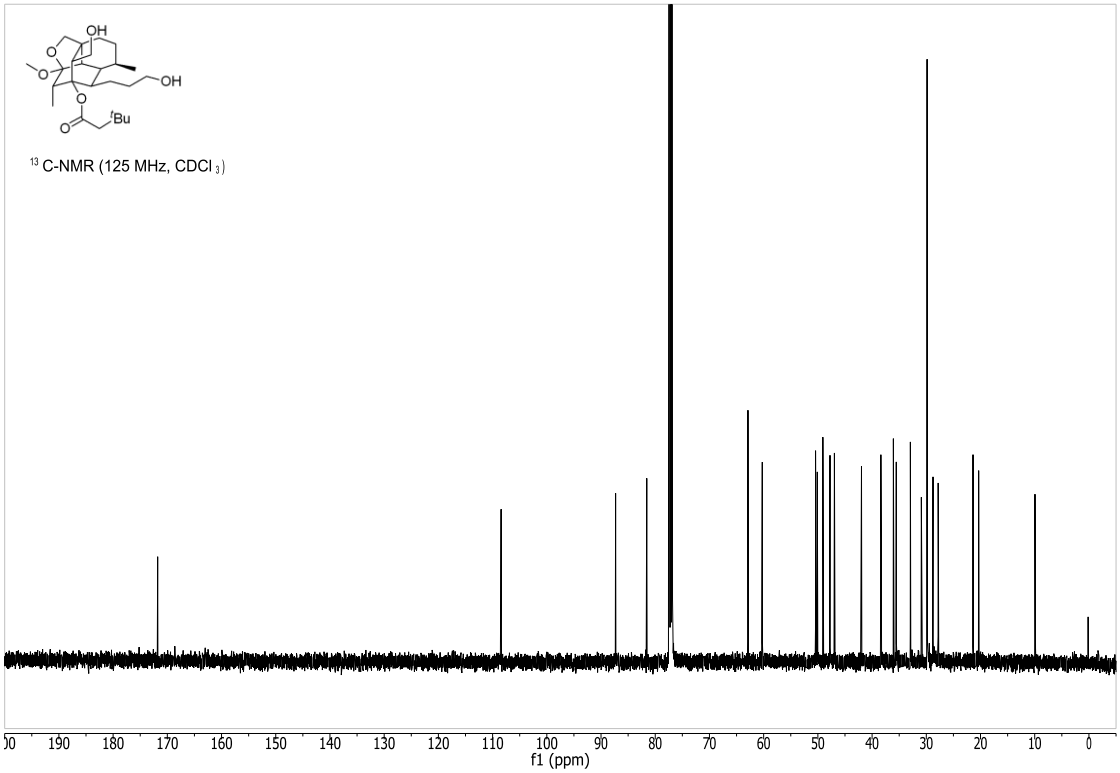

OH
OH
O
CF3
1 H-NMR (600 MHz, CDCl 3)
f1 (ppm)

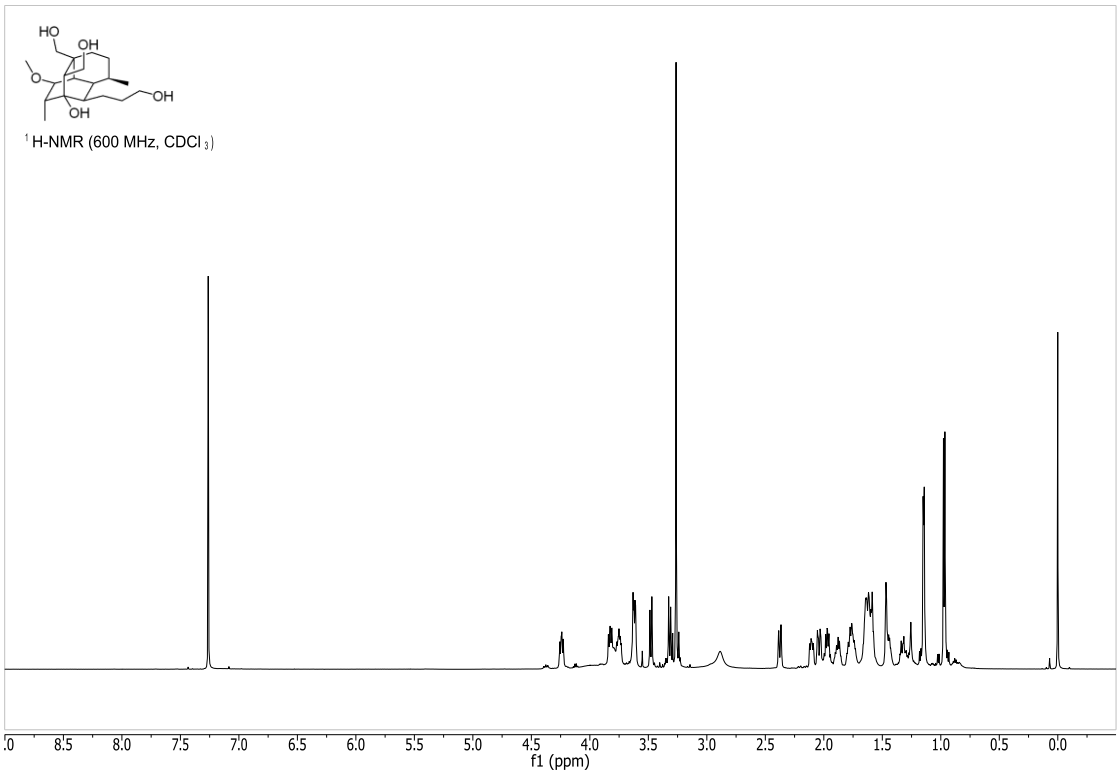

OH
OH
O
CF3
13 C-NMR (125 MHz, CDCl 3)
f1 (ppm)

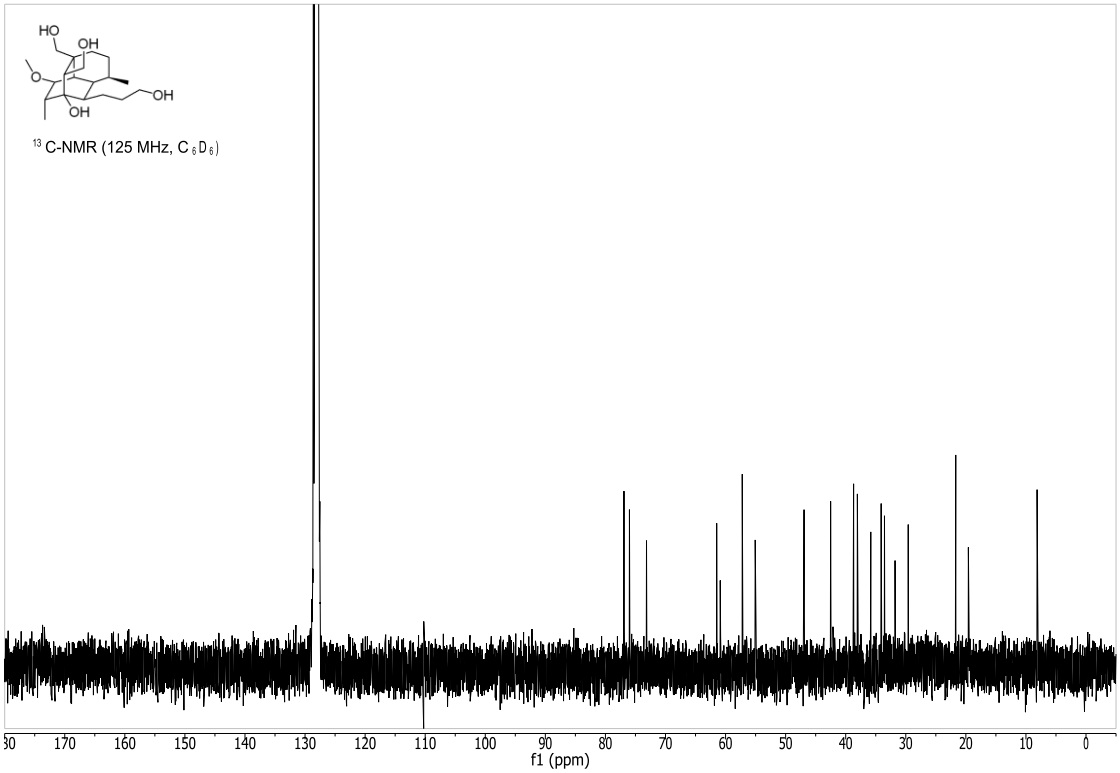

OH
O
O
OH
O
tBu
1 H-NMR (600 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

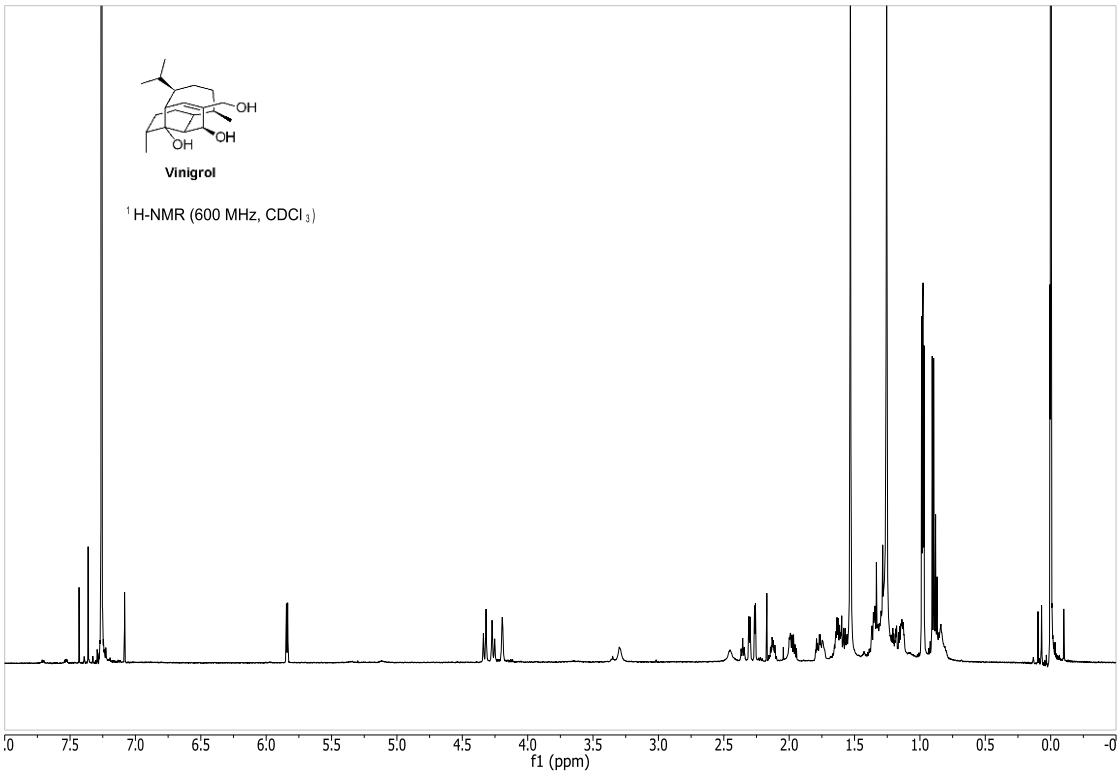

OH
O
O
OH
O
tBu
13 C-NMR (125 MHz, CDCl 3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

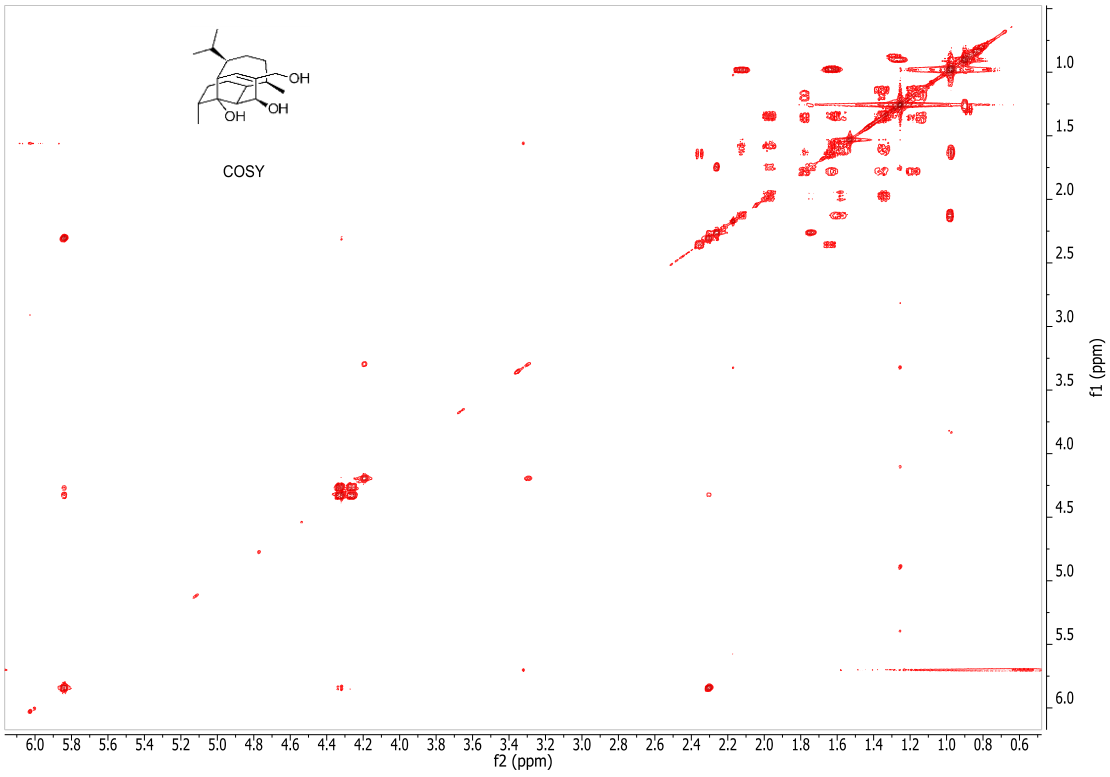

OH
O
O
OH
O
tBu
1 H-NMR (500 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

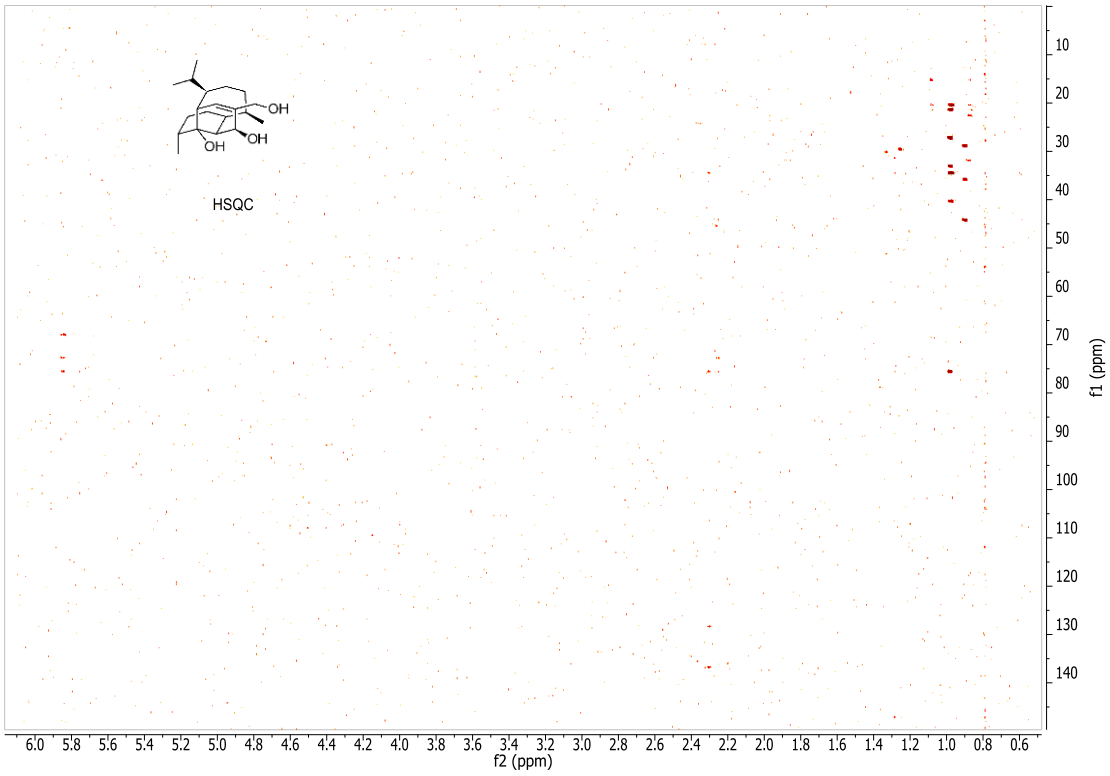

OH
O
O
OH
O
tBu
13 C-NMR (125 MHz, CDCl 3)
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


HO
OH
O
OH
OH
1 H-NMR (600 MHz, CDCl 3)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


HO
OH
O
OH
OH
13 C-NMR (125 MHz, C 6 D 6)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


OH
OH
OH
Vinigrol
^{1}H-NMR (600 MHz, CDCl$_3$)
f1 (ppm)


OH
OH
OH
COSY
f2 (ppm)
f1 (ppm)


OH
OH
OH
HSQC
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f2 (ppm)

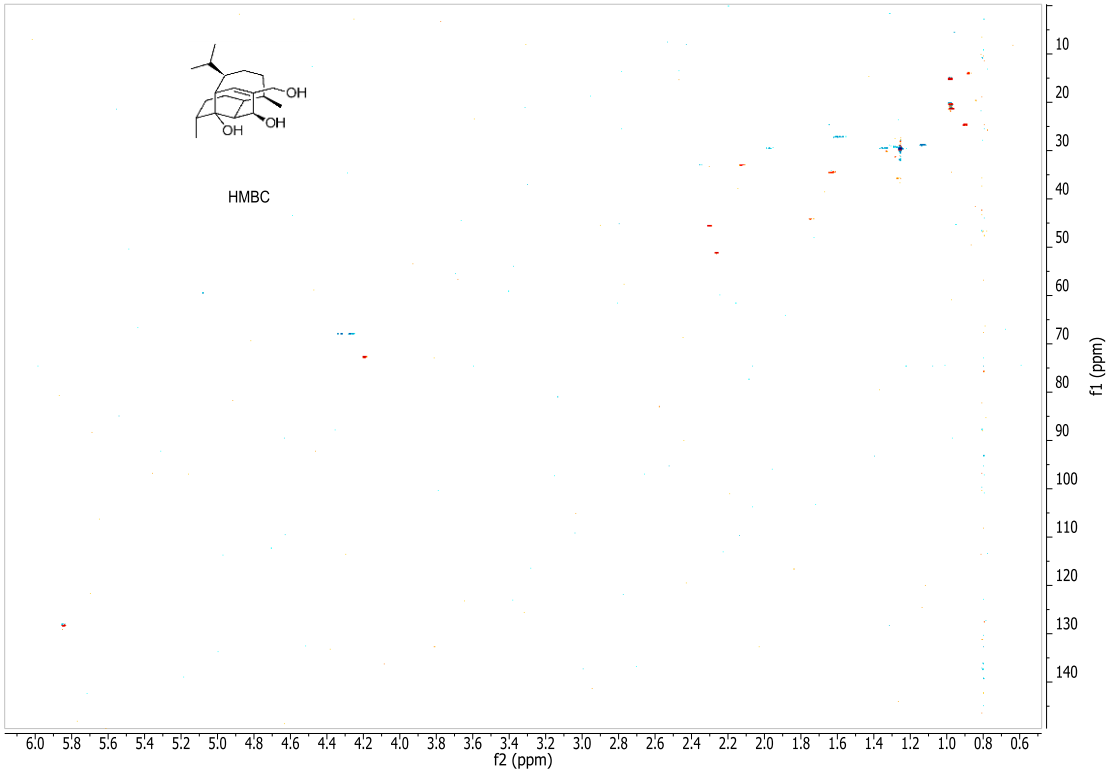
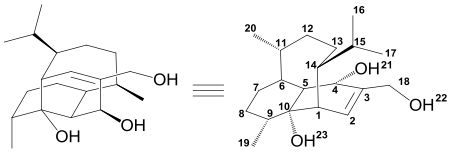

OH
OH
OH
HMBC
10
20
30
40
50
60
70
80
90
100
110
120
130
140
f1 (ppm)
6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6
f2 (ppm)

Table A3.5. 2D-NMR Data of Vinigrol



Position	δ ^{13}C (ppm)	δ ^{1}H (ppm)	Type	COSY correlations	HMBC correlations
1	45.8	2.30	CH	H-2, H-18a, H-18b	C-3, C-2, C-10, C-15
2	128.4	5.84	CH	H-18a, H-18b, H-1	C-10, C-4, C-18, C-1
3	136.4		Cq		
4	72.8	4.19	CH	H-21	
5	51.3	2.26	CH	H-4, H-6	C-4, C-1
6	44.2	1.74	CH	H-5, H-7b	
7a	29.6	1.35	CH_2	H-7b, H-8b	
7b		1.97		H-6, H-8a, H-8b, H-7a	
8a	27.3	1.59	CH_2	H-9, H-7b, H-7a, H-8b	
8b		1.59		H-8a, H-7b, H-7a	
9	33.1	2.12	CH	H-8a, H-8b, H-19	
10	75.6		Cq		
11	35.9	1.26	CH	H-20	
12a	28.9	1.13	CH_2	H-12b	
12b		1.34		H-12a	
13a	28.6	1.19	CH_2	H-14, H-13b	
13b		1.35		H-14, H-13a	
14	40.4	1.77	CH	H-15, H-13b, H-13a	
15	34.7	1.63	CH	H-14, H-16, H-17	
16	21.5	0.98	CH_3	H-15	C-14, C-15, C-17
17	20.5	0.98	CH_3	H-15	C-14, C-15, C-16
18a	67.9	4.26	CH_2	H-2, H-18b, H-22, H-1	
18b		4.33		H-2, H-18a, H-22, H-1	
19	15.3	0.98	CH_3	H-9	C-10, C-9,C-8
20	24.9	0.90	CH_3	H-11	C-6, C-11, C-12
21		3.30	OH	H-4	
22		2.46	OH	H-18a, H-18b	
23		1.99	OH		

Table A3.6. Vinigrol's ^{1}H NMR Data Comparison (δ in ppm)

Our synthetic sample ($CDCl_3$, 600 MHz) (multiplicity, coupling constant)	**Baran's sample ($CDCl_3$, 600 MHz)[2] (multiplicity, coupling constant)**
5.84 (d, 5.6 Hz)	5.83 (d, 5.5 Hz)
4.30 (AB q, 12.0 Hz)	4.30 (AB q, 12.0 Hz)
4.19 (s)	4.20 (s)
3.30 (bs)	3.40 (bs)
2.45 (bs)	2.65 (bs)
2.30 (d, 5.6 Hz)	2.30 (d, 5.4 Hz)
2.26 (d, 3.9 Hz)	2.25 (d, 3.7 Hz)
2.15 – 2.09 (m)	2.15– 2.09 (m)
2.03 – 1.93 (m)	1.99 – 1.93 (m)
1.81 – 1.71 (m)	1.80 – 1.70 (m)
1.66 – 1.53 (m)	1.65 – 1.50 (m)
1.40 – 1.10 (m)	1.40 – 1.05 (m)
1.00 – 0.95 (m)	1.00 – 0.95 (m)
0.90 (d, 6.8 Hz)	0.90 (d, 6.8 Hz)

Table A3.7. Vinigrol's ^{13}C NMR Data Comparison (δ in ppm)

Our synthetic sample ($CDCl_3$)	**Baran's sample ($CDCl_3$, 150 MHz)[2]**
136.8	136.5
128.4	128.4
75.6	75.5
72.8	72.8
67.9	67.9
51.3	51.1
45.8	45.5
44.2	44.2
40.4	40.2
35.9	35.8
34.7	34.5
33.1	33.0
29.6	29.6
29.0	28.9
28.7	28.6
27.3	27.2
24.9	24.8
21.5	21.5
20.6	20.5
15.4	15.3

References

(1) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Letters.* **1996**, 37, 6787-6790.

(2) Maimone, T. J.; Shi, J.; Ashida, S.; Baran, P.S. *J. Am. Chem. Soc.* **2009**, 131, 17066-17067.